"A PROSPECTIVE, RANDOMIZED, OPEN LABEL, COMPARATIVE STUDY OF RESVERATROL AS AN ADD ON THERAPY IN SYSTEMIC HYPERTENSION"

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DOCTOR OF MEDICINE

IN

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CERTIFICATE

This is to certify that the dissertation entitled, **"A PROSPECTIVE, RANDOMIZED, OPEN LABEL, COMPARATIVE STUDY OF RESVERATROL AS AN ADD ON THERAPY IN SYSTEMIC HYPERTENSION"** submitted by **Dr.G.SELVAM,** in partial fulfilment for the award of the degree of Doctor of Medicine in Pharmacology by The Tamilnadu Dr.M.G.R.Medical University, Chennai is a Bonafide record of the work done by him in the Institute of Pharmacology, Madras Medical College during the academic year 2016-2019.

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DECLARATION

I, **Dr.G.SELVAM,** solemnly declare that the dissertation titled **"A PROSPECTIVE, RANDOMIZED, OPEN LABEL, COMPARATIVE STUDY OF RESVERATROL AS AN ADD ON THERAPY IN SYSTEMIC HYPERTENSION"** has been prepared by me and submitted to Tamil Nadu Dr. MGR Medical University, Chennai in partial fulfilment of the rules and regulations for the M.D degree examination in Pharmacology.

Date: **Dr. G. SELVAM**

Place:

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PLAGIARISM CERTIFICATE

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Introduction

INTRODUCTION

Hypertension is long term medical condition in which the blood pressure is persistently elevated in the arteries.

High arterial blood pressure is one of the most important public health problems in both developing and developed countries. Estimated prevalence of hypertension in India is 29.8% as on 30th April 2014. are usually life style and genetic factors(1). Other factors that are associated with developing hypertension are excess salt intake, sedentary life style, obesity, smoking and excessive alcohol intake.

High blood pressure is usually presents as asymptomatic. Even though it is easily detectable, easily treatable it often leads to severe complication if not diagnosed and treated early.

Long term high blood pressure if untreated is a major risk factor for developing cardiac complication such as left ventricular hypertrophy, left ventricular dysfunction, congestive cardiac failure, ventricular arrhythmias, myocardial infarction and sudden death(2).

Other complications due to hypertension include stroke, hypertensive retinopathy, hypertensive nephropathy, aortic dissection etc. Cardiac complications are one of the major causes of morbidity and mortality in hypertension. Preventing these complications is the major goal of treatment (3).

In India death due to cardio vascular disease is 272 per 100,000 populations which is relatively high compared to the world average of 235 per 100,000 populations. Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary artery disease death in India.

According to new ACC and American Heart Association AHA guide lines November 13, 2017.

- Normal : Blood pressure is less than 120/80 mmHg
- Elevated blood pressure is systolic between 120 – 129 and diastolic less than 80
- Stage 1 : Hypertension is systolic between 130 – 139 or diastolic between 80 – 89
- Stage 2 : Hypertension is systolic at more than 140 or diastolic more than 90 mmHg

Hypertension further classified as primary hypertension and secondary hypertension. Of these 90 to 95% hypertensive are primary hypertension and are due to non-specific factors such as life style factors and genetic factors [(4)]. Life style factors that increase the risk of developing hypertension are excessive salt intake in the diet, excess body weight, smoking and alcohol use.

Remaining 5 to 10% of cases are classified as secondary hypertension which is due to other systemic diseases such as chronic kidney diseases, narrowing of the kidney arteries, an endocrine disorder or due to use of birth control pills[(5)].

Life style changes and medication will reduce blood pressure and reduce the risk of complications due to high blood pressure. Life style modifications are weight loss, decreased salt intake, physical exercise and a healthy diet. If life style modifications do not reduces high blood pressure then medication should be added to reduce high blood pressure.

Several classes of medications collectively known as antihypertensive drugs are available for treating high blood pressure.

First line medication for treating hypertension are thiazide – diuretics, calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers. These medications either used as a single drug therapy or as a combination therapy based on efficacy and tolerability [(6)].

Resveratrol is a naturally occurring flavonoid phytoalexin having antioxidant properties. It is increasingly used in the treatment of various diseases due to its cardio protective, ant diabetic and neuroprotective effects. In addition to this some studies have shown resveratrol to have vasoprotective properties[(7)].

EFSA as categorized resveratrol as a food supplement and it can be taken without a doctor prescription or recommendation. Resveratrol appears to control high blood pressure when added to a standard antihypertensive treatment by increasing the Nitric oxide production, which is an endogenous potent vasodilator[(8)].

Several animal studies and clinical trials suggest that resveratrol reduces blood pressure significantly when given as add on therapy to antihypertensive drugs[9]. Hence the open label prospective, randomized, parallel group study is undertaken to find out the efficacy and tolerability of resveratrol as an add on therapy to standard antihypertensive regimen in reducing blood pressure.

Review of Literature

REVIEW OF LITERATURE

Hypertension is a chronic condition and plays a major role in causation of coronary heart diseases, stroke and other vascular complications. Hypertension commonly referred to as “high blood pressure” is a medical condition in which the blood pressure is chronically elevated. Hypertension is a major public health challenge to population in socio – economic and epidemiological transition.

A practical definition of hypertension is the level of BP at which the benefit of treatment outweighs the cost and hazard.

DEFINITION OF HYPERTENSION

CATEGORY	SYSTOLIC BP	DIASTOLIC BP
BP OPTIMOL	< 120	< 80
NORMAL	< 130	85
HIGH NORMAL	130 – 139	85 - 89

GRADES OF HYPERTENSION

GRADE 1 (mild)	140- 159	90- 99
GRADE 2 (moderate)	160 – 179	100 – 109
GRADE 3 (severe)	>180	>110

ISOLATED SYSTOLIC HYPERTENSION

GRADE 1	140 -159	< 90
GRADE 2	>160	< 90

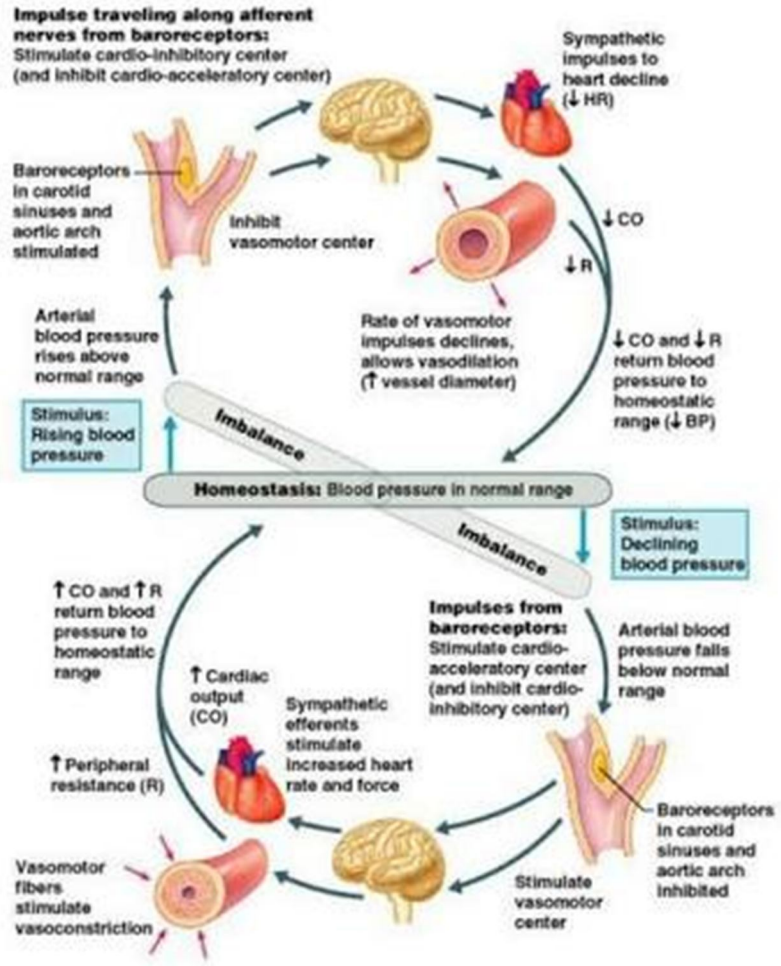
AETIOLOGY:

In 95% of hypertensive patient no specific underlying cause can be found and they are called as essential hypertension.

There are many factors that may contribute to the development of essential hypertension e.g.: Renal dysfunction, endothelial dysfunction, peripheral resistance vessel tone, autonomic tone insulin resistance and neurohumoral factors[(9)]. Environmental factors that cause essential hypertension are high salt intake, obesity, lack of exercise, heavy consumption of alcohol and impaired intrauterine growth. Stress is also known to cause hypertension.

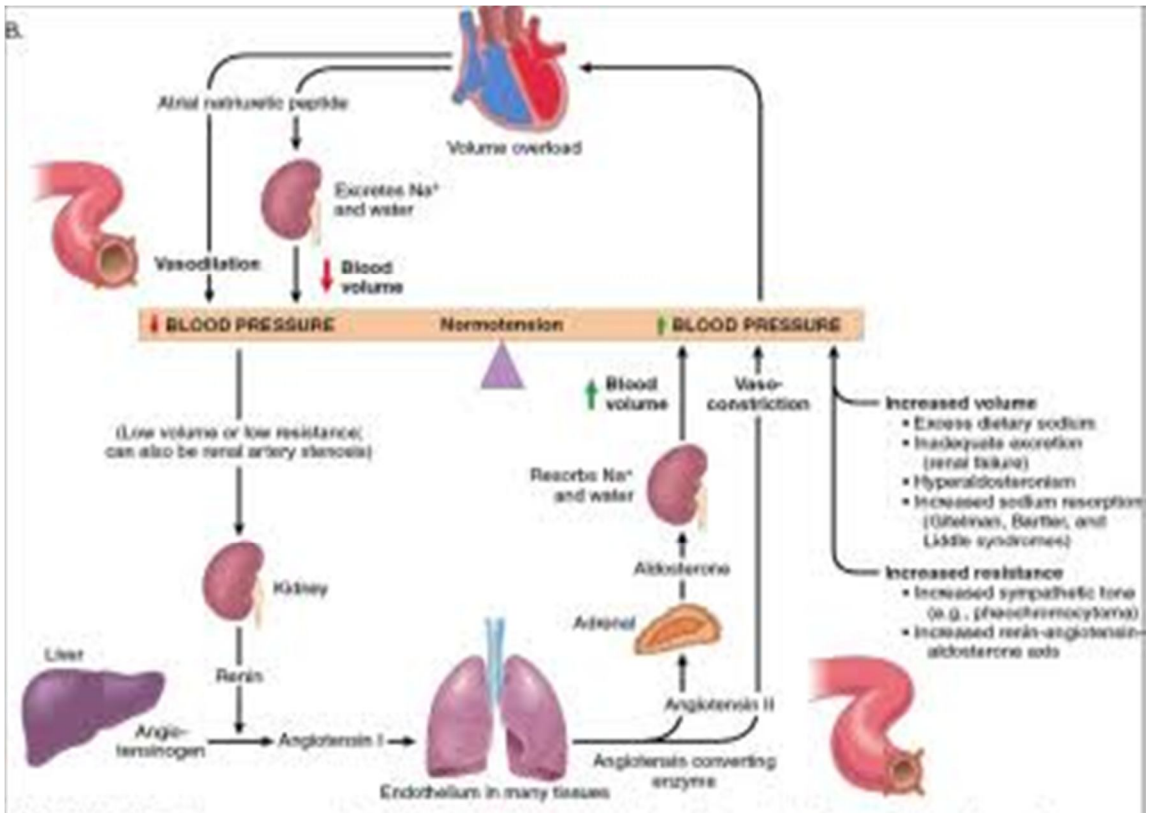
In another 5% of cases hypertension is may be due to a specific disease or abnormality leading to sodium retention and / or peripheral vasoconstriction. This is called as secondary hypertension[(11)].

The major risk factor for development of strokes, heart attacks, heart failure, arterial aneurysm and chronic renal failure is persistent hypertension. Even moderate persistent elevation of arterial blood pressure leads to shortened life expectancy. At severely high blood pressure, a person cannot be expected to live not more than a few years unless appropriately treated [(13)].



SALT SENSITIVITY:

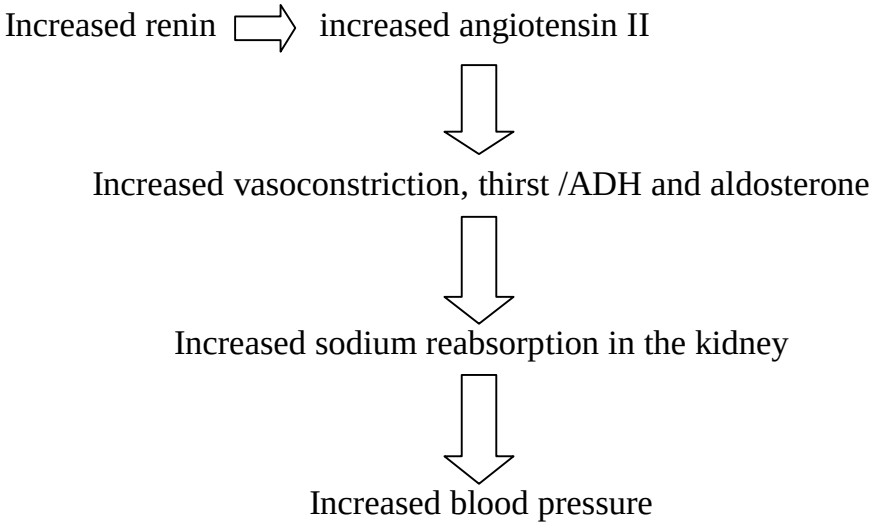
Among the environmental factors that cause hypertension, sodium is the most important. There is increasing evidence to suggest that a high salt intake (i.e. 7.8g per day) increases blood pressure proportionately. Approximately 60% of the essential hypertensive populations are due to high sodium intake [(14)]. In fact increasing the amount of salt in a person's bloodstream causes the body to draw more water, thereby increasing the pressure on the blood vessel walls.



ROLE OF RENINS:

Renin is a hormone secreted by the juxtaglomerular cells of the kidney and linked with aldosterone in a negative feedback loop. The level of renin activity is very high in hypertensive subjects compared to normotensive individuals[(15)]. But some hypertensive patients have low level of renin and it is known as low renin hypertension. It is commonly seeing in African American and Japanese. These people will respond to diuretic therapy than drugs that interfere with renin – angiotensin system.

High renin levels predispose to hypertension.



GENETICS:

Hypertension is one of the most common complex disorders, with genetic heritability averaging 30%. Data supporting this view emerge from animal studies as well as in population studies in humans[(18)].

Most of these studies support the concept that the inheritance is probably multifactorial or that a number of different genetic defect each have an elevated blood pressure as one of their phenotype expression. More than 50 genes have been examined in association studies with hypertension, and the number is constantly growing.

ETIOLOGY OF SECONDARY HYPERTENSION:

Approximately 5% of patients in the world have secondary to identifiable specific cause. Secondary hypertension should be always suspected in patients in whom hypertension develops after the age of 50 years or at an early age, and in those previously well controlled blood pressure but later become refractory to treatment[22].

Hypertension resistance to three antihypertensive medications is another clue, although diabetes patients need multiple medications. Secondary causes for hypertension include genetic syndromes, kidney disease, renal vascular disease, primary hyperaldosteronisim, Cushing syndromes, pheochromocytoma, coarctation of the aorta and hypertension associated with pregnancy, estogen use, hypercalceamia and other medication[24].

Genetics causes

Hypertesion is due to mutation in single genes, inherited on a mendelian basis. Although it is rare, these conditions provide more insight into blood pressure regulation and possible genetic basis of essentials hypertension[18].

Autosomal dominant cause for early onset hypertension with normal or high aldosterone and low renin levels is caused by the formation of a chimeric gene encoding both the enzymes responsible for the synthesis of aldosterone and for synthesis of cortical[27]. As a consequence, aldosterone synthesis which is driven by ACTH can be suppressed by exogenous cortisol. In the syndrome of

apparent mineralocorticoid excess, early onset hypertension with hypokalemic metabolic alkalosis is inherited on an autosomal recessive basis[31]. Even thought plasma renin is low and plasma aldosterone level is very low, aldosterone antagonists are effective in controlling hypertension in these patients. In these patients loss of the enzyme 11 beta – hydroxysteroid dehydrogenase, which normally metabolizes cortisol and protects the mineralocorticoid receptor in the distal nephron due to inappropriate glucocorticoid activation is lost. Similarly licorice causes increased blood pressure through inhibition of 11 beta - hyroxysteroid dehydrogenase [32].

The syndrome of hypertension seen in pregnancy is inherited as an autosomal dominant trait. In pregnancy induced hypertension mutation in the mineralocorticoid receptor makes them abnormally responsive to progesterone and paradoxically to spironolactone.

Liddles syndrome is an autosomal dominant condition in which early onset hypertension is associated with hypokalemia, low renin, and low aldosterone levels [34]. This is caused by a mutation of the epithelial sodium channel of the distal nephron.

Renal diseases:

Renal parenchymal diseases are the most common cause of secondary hypertension. Increased intravascular volume or increased activity of the renin – angiotensin – aldosterone system is the cause.

Renal vascular hypertension:

Renal artery stenosis is present in 1 to 2% of all the hypertensive patients of the world. Atherosclerosis is the most common cause but in women below 50 years fibromuscular dysplasia should be suspected.

The mechanism of hypertension in these patients is due to excessive renin release due to decrease in renal perfusion pressure. In single kidney disease or bilateral lesion patient's decreased natriuresis contributes to hypertension. Activation of the renal sympathetic nerves is also important.

Renal vascular hypertension should be suspected when

1) when hypertension develops before age 20 or after age 50 years.
2) when hypertension is resistance to three or more antihypertensive drugs.
3) if epigastric or renal artery bruits are felt
4) in atherosclerotic diease of the aorta or peripheral arteries
5) if there is an abrupt increase in the level of serum creatinine after giving angiotensin – converting enzyme (ACE) inhibitors, or
6) if episodes of pulmonary edema with abrupt increase in blood pressure are seen.

There is no ideal screening test for renal vascular hypertension. If suspicion is high renal arteriography is the definitive diagnostics test. Where suspicion is moderate to low, noninvasive angiography using magnetic resonance (MR) or CT can be done[(44)].

Doppler sonography has good specificity but lacks sensitivity. Contrast agent gadolinium used in MR angiography is contraindicated in patient when estimated glomerular filtration rate (eGFR) is less than 30 ml / min. But in young patients with fibromuscular disease, angioplasty is very effective.

Correction of the stenosis in some patients will reduce the number of medications required to control blood pressure and protect the kidney function.

The extent of preexisting parenchymal damage of the affected and contralateral kidney will have a significant influence on both blood pressure and kidney function out comes following revascularization[33].

Angioplasty and stenting may be superior to medical therapy in some patients. A reasonable approach always is to continue medical therapy as long as hypertension can be well controlled and there is no progression of kidney diseases. A statin should always be added to the treatment regime.

Endovascular intervention should be considered in patients only when uncontrollable hypertension, progressive kidney diseases, or episodic pulmonary edema are present [50].

However, multiple studies have failed to identify the overall advantage of stenting over antihypertensive medical management in patients with atherosclerotic renal artery stenosis. Although many drugs modulating the renin-angiotensin system have improved the success rate of medical management of

hypertension due to renal artery stenosis, still they may trigger hypotension and kidney dysfunction in persons with bilateral diseases.

Primary hyperaldosteronism:-

Hyperaldosteronism is suggested when the plasma aldosterone concentration is high and low plasma renin activity. However the plasma aldosterone/ renin ratio is not a screening test for primary hyperaldosteronism.

Adrenal adenoma or bilateral adrenal hyperplasia is responsible for hyperaldosteronism associated in patients with secondary hypertension. Screening is always done in patients with resistant hypertension and in those with spontaneous or thiazide-induced hypokalemia or family history of primary hyperaldosteronism.

While evaluating for hyperaldosteronism, drugs that alter renin and aldosterone levels such as ACE inhibitors, angiotensin receptor blockers, diuretics, beta blockers and clonidine should be discontinued for two weeks[(17)]. Spironolactone and eplerenone should be held for 4 weeks.

Patients can be treated with Calcium Channel and alpha receptor blockers to control blood pressure during this drug wash out period. Patients with a plasma aldosterone levels greater than 16ng/dl and an aldosterone/renin ratio of 30 or more might require further evaluation for primary hyperaldosteronism.

Cushing Syndrome:

About 80% of patients with cushing syndrome will have hypertension. Excess glucocorticoid is the cause along with increased salt and water retention due to increased angiotension level.

Pheochromocytoma:

Pheochromocytoma is an uncommon disease and is found in less than 0.1% of all the hypertensive patients in the world. However autopsy studies indicate that pheochromocytoma are very often undiagnosed in life.

Blood pressure elevation in pheochromocytoma is caused due to excessive catecholamines which results in vasoconstriction of arterioles, and increased in cardiac output and renin release. Hypertensive crisis in pheochromocytoma may be precipitated by a variety of drugs including tricyclic antidepressant, anti dopaminergic agents, metoclopramide and naloxone[(52)].

Coarctation of the aorta:

Evidence of radial femoral delay should be sought in all younger patients with hypertension.

Hypertesion associated with pregnancy:

Hypertension occurring or worsening during pregnancy including preeclampsia and eclampsia is one of the major and common causes of maternal and fetal morbidity and mortality. Auto antibodies which activate the angiotensin II type 1 receptor have been implicated in preeclampsia patients[(48)].

Estrogen use:

A slight increase in blood pressure occurs in most women taking oral contraceptives. However a more significant increase in blood pressure of above 140/90mmHg is noted in about 5% of obese women older than age 35 years and who have been treated for more than 5 years[(24)]. This is due to increased hepatic synthesis of angiotensinogen. Postmenopausal esterogen usually does not cause hypertension'

Other causes of Secondary Hypertension:-

Hypertension has also been associated with hypercalcemia, acromegaly, hyperthyroidism, hypothyroidism, baroreceptor denerbation, compression of the rospralventrolateral medulla and increased intracranial pressure[(43)]. Some drugs may cause hypertension such as cyclosporine, tacrolimus, decongestant, NSAIDs, cocaine and alcohol.

When to refer:

Referral to a hypertension specialist should always be considered in case of severe resistant or early / late onset hypertension or when secondary hypertension is suggested by screening.

Only in a small minority of patients with elevated arterial pressure, can a specific cause be identified. These individuals will probably have an endocrine or renal defect that, if corrected, pressure will come back to normal value [(51)].

PATHOPHYSIOLOGY:

Hypertension is a wildly prevalent disease and a major risk factors for adverse CVS events including CAD, PVD, HF and CKD. Studies show there is a continues relationship between high blood pressure and adverse cardiovascular outcomes including death. Previously high diastolic blood pressure was the indicator for initiating anti-hypertensive treatment but now even elevated systolic blood pressure alone is also sufficient enough to start anti-hypertensive treatment, particularly in elderly people.

One of the major obstacles in the treatment of hypertension is the largely asymptomatic nature of the disease, even in patient with marked elevation in systolic blood pressure. This disconnect between symptoms and long term adverse consequences has earned hypertension the designation “silent killer”. Some people begin to exhibit symptoms only after doing exercises. In this type of people hypertension put them at major risk for developing coronary artery disease, stroke and heart failure. Thus, effective strategies for detection and management of hypertension are critical elements in the primary and secondary prevention of cardiovascular diseases.

Fortunately there are many number of drugs available to treat patient with hypertension. These drugs can be given initially as a single drug. However the progressive nature of hypertension characteristically leads to the use of multi drug treatment [(28)]. Although the clinical end points of treatment can vary from patient to patient, the principle aim of treatment of hypertension is to reduce the measured

blood pressure below 140 mm Hg mercury for systolic and less than 90 mm Hg for diastolic blood pressure.

Clinically hypertension has been categorized as primary or secondary hypertension. Essential hypertension is the one in which the cause of elevated blood pressure is unknown in 90-95% of the hypertensive population. The cause of essential hypertension more likely multi factorial, including both genetic factors and environmental factors such as alcohol consumption, obesity and high salt intake [33]. Secondary hypertension refers to patient in whom increased blood pressure can be due to a defined cause. Example of secondary hypertension includes primary hyperaldosternism, use of oral contraception, intrinsic renal diseases and renovascular diseases.

Blood pressure is usually determined by the product of heart rate, stroke volume and systemic vascular resistance. Heart rate is mainly determined by sympathetic activity. Preload, afterload and contractility of heart determines stroke volume. Systemic vascular resistance reflects the aggregate vascular tone of the arteriole subdivision of the systemic circulation. The pharmacological approach to the treatment of both primary and secondary hypertension requires an understanding of the physiology of normal blood pressure regulation and the mechanism that could be responsible for hypertension in individual patients.

CARDIAC FUNCTION:

One important mechanism for persistence high blood pressure is due to primary elevation in cardiac output ('high output' hypertension). A 'hyperkinetic' circulation can occur due to excessive sympathoadrenal activity and / or increased sensitivity of the heart to basal levels of neurohumoral regulaters. The hemodynamic pattern of pump based hypertension (ie, increased cardiac output (CO) with normal systemic vascular resistance (SVR) is most often seen in younger patients with essential hypertension. This pattern can then affect vascular wall tone and then hemodynamic profile in which the principle cause of disease appears to shift to the peripheral vasculature. This high output hypertension patients are treated with β – adrenoceptive antagonist.

VASCULAR FUNCTION:

Vascular resistance based hypertension (ie normal CO with increased SVR) is a common mechanism underline hypertension in the elderly people. In individuals with this form of hypertension, it is hypothesized that the vasculature is abnormally responsive to sympathetic stimulation, circulating factors or local regulation of vascular tone. The abnormal responsiveness of the vasculature may be mediated in parts by endothelial damage or dysfunction, which is known to disrupt the normal equilibrium between local vasodialating (eg. Nitric oxide) and vasoconstructive (eg. Endothelin) factors. In addition ion channel defects in vascular smooth muscle can cause abnormal elevation in basal vasomotor tone that result in increased systemic vascular resistance[(28)]. Vascular resistance – based hypertension may present as a predominant elevation of systolic blood

pressure. Studies have demonstrated the effectiveness of thiazide diuretic in this population making such agents the preferred initial treatment.

RENAL FUNCTION:

Abnormalities of renal function can lead to the development of systemic hypertension. Volume based hypertension develops due to excessive retention of sodium and water. Glomerular injury caused by renal parenchymal disease will reduce functional nephron mass and/ or excessive secretion of renin which will lead to abnormal increase in intra vascular volume [(42)].

Sometimes, ion channel mutation can impair normal sodium excretion. Decreased renal blood flow due to renal vascular diseases (eg. Renal artery stenosis fibromuscular dysplasia, vasculitis or external compression) will lead to decreased perfusion pressure of kidneys. Decreased perfusion will lead to excessive secretion of renin by juxtaglomerular cells, which in turn lead to increased production of angiotension II and aldosterone [(62)]. This will increase vasomotor tone and Na^+ and H_2O retension, leading to a hemodynamic profile in which both CO and SVR increased.

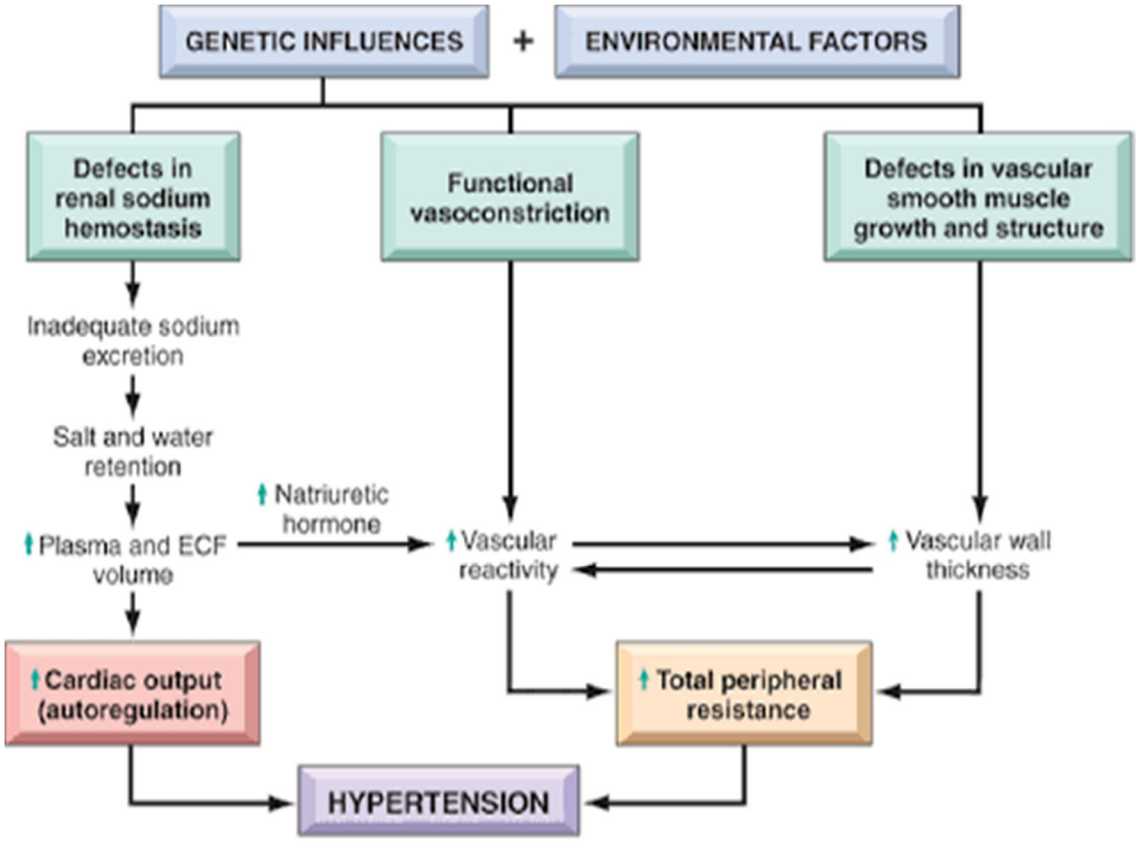
NEUROENDOCRINE FUNCTION:

Abnormal function of the endocrine system including dysfunction of central regulation of basal sympathetic tone, atypical stress response, abnormal responses to signals from baroreceptors and intravascular volume receptors and excessive production of hormones that act to regulate the circulation can alter cardiac, vascular and/ or renal functions leading to increased systemic blood

pressure[35]. Example of endocrine abnormalities associated with systemic hypertension include excessive secretion of aldosterone by the adrenal cortex [primary aldosterone] and excessive production of thyroid hormone (hyperthyroidism).

Most of the secondary mechanisms associated with hypertension are generally fully understood, and are outlined as secondary hypertension.

However, those associated with essential (primary) hypertension are far less understood. What is known is that cardiac output is raised early in the disease course, with total peripheral resistance (TPR) normal[42]. After sometime the time cardiac output drops to normal level but TPR is increased.



Three theories have been proposed to explain this:

Theory 1:

Inability of the kidneys to excrete sodium resulting in nateriuretic factor such as Atrial Natriuretic Factor being secreted to promote salt excretion with the side effects of raising total peripheral resistance.

Theory 2:

An overactive renin – angiotension system leads to vasoconstriction and retention of sodium and water. The increased in blood volume leads to hypertension.

Theory 3:

An overactive sympathetic nervous system leading to increased stress responses. It is also known that hypertension is highly heritable and polygenic (caused by more than one gene) and a few candidate genes have being postulated in the etiology of the condition.

APPROACH TO NEWLY DIAGNOSED HYPERTENSION:

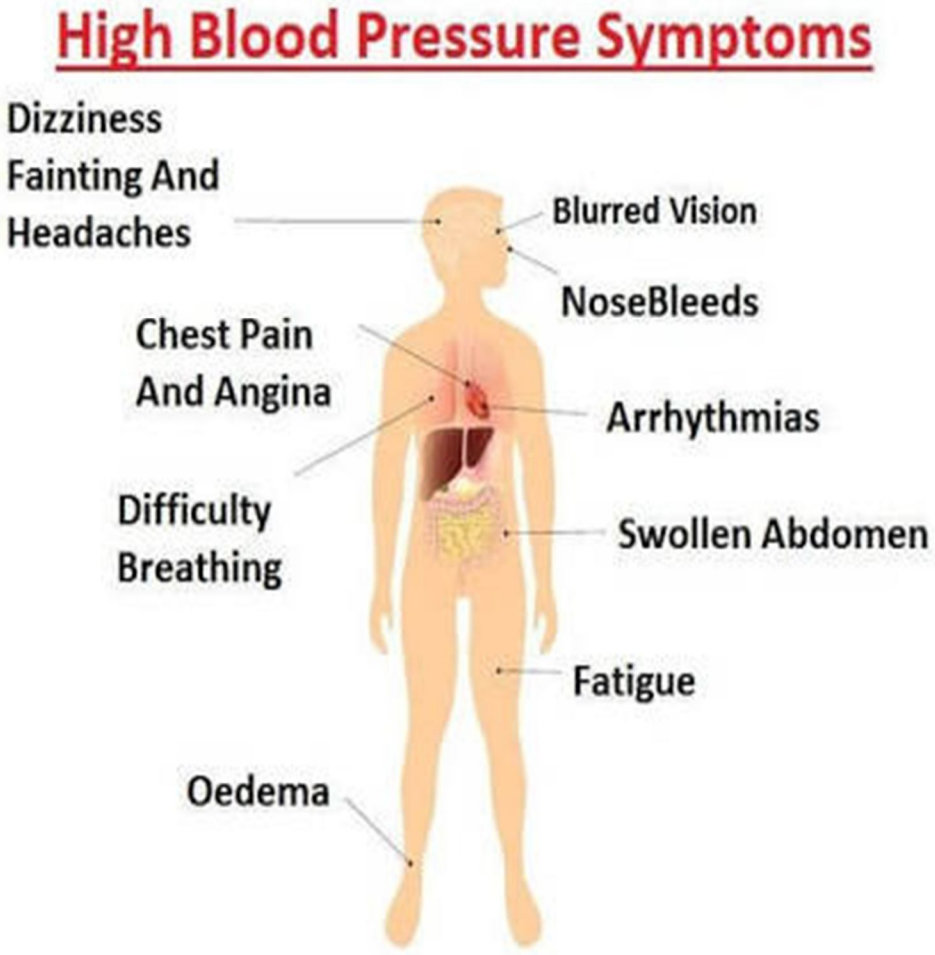
Hypertension patients are usually asymoptomatic and they are diagnosed usually by routine examination or when a complication arises.

The objective of the intial evaluation of patients with high BP reading are

- To obtain accurate blood pressure measurement
- To identify any underlying cause and contributory factors.
- To access other risk factor especially cardiovascular risk.

- To detect any complication those are already present eg: end organ damage.
- To identify any comorbidity that may influence the choice of antihypertensive therapy.

These are attained by careful history taking, clinical examination and some simple investigation.



BLOOD PRESSURE MEASUREMENT:

Blood pressure is recorded usually in sitting position. The reading at which the sounds are first heard is taken as systolic pressure. The pressure reading at which the sounds disappear is taken as diastolic pressure. Both systolic and diastolic pressures should be measured at least three times. Of the three readings the lowest reading should be noted.

MAGNITUDE OF THE PROBLEM:

Even though blood pressure can be measured easily, it took several years to realize that this arterial hypertension is a frequent and major worldwide health problem[(18)].

INCIDENCE:

World wide , it was estimated that high blood pressure caused more than 7.5 million deaths that is above 12.8 percent of the total of all annual deaths. Hypertension is a major risk factor for ischaemic heart diseases and coronary heart diseases as well as hemorrhagic strokes. Other complications due to persistence raised blood pressure are heart failure, peripheral vascular disease, renal impairment, visual impairment and retinal hemorrhage. Reducing systolic and diastolic blood pressure below 140/90 is associated with a reduction in cardio vascular complications[(22)]. The prevalence of raised blood pressure is around 40% for both sexes and also in low, lower middle and upper middle – income countries. In high income countries it is above 35% for both sexes.

PREVALENCE IN INDIA:

Prevalence of hypertension is above 17 to 21 % throughout India. Even though hypertension was prevalent in all educational levels it is much higher in higher educational level of states in India such as Kerala and Tamilnadu.

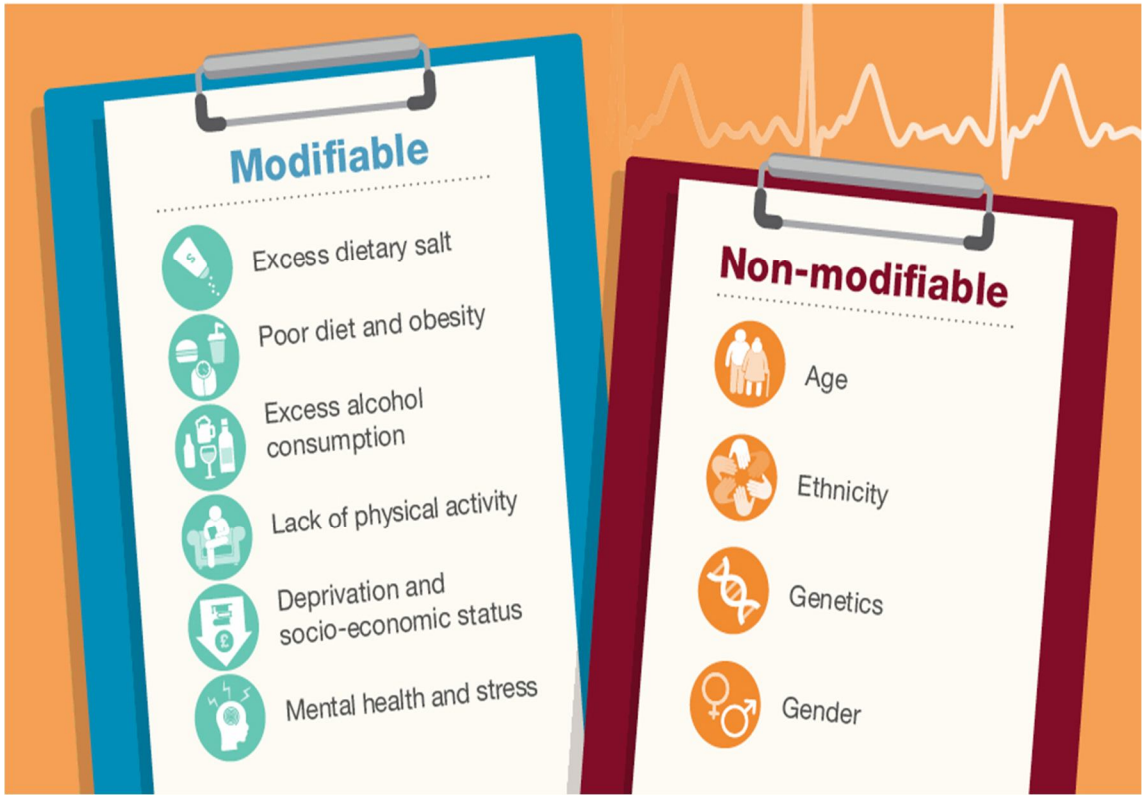
PREVENTION OF HYPERTENSION

PRIMARY PREVENTION:

Eventhough control of hypertension can be achieved by medication the ultimate goal in general is primary prevention. Primary prevention has been defined as “all measures to reduce the incidence of disease in a population by reducing the risk of onset “

Non pharmacotherapeutic intervention to reduce arterial hypertension are;

- Reduction of salt intake that is less than 5gm /day
- Reduction in fat intake
- Avoidance of high alcohol intake
- Weight reduction
- Physical exercise
- Behavioral changes such as reduction of stress and quitting smoking, life style modification , and doing yoga and taking medications



SECONDARY PREVENTION:

To detect and control high blood pressure in affected individual is the goal of secondary prevention.

Early reduction of hypertension is a major problem because most of the patients are asymptomatic until an organ damage has occurred. Therefore screening is the only effective method of diagnosis of hypertension.

TREATMENT

In essential hypertension, we cannot treat the cause because we do not know what is the cause for high blood pressure. Instead we try to bring down the persistently high blood pressure to normal levels. The main objective of treatment is to get a blood pressure below 140/90, because control of hypertension as shown to reduce the incidence of stroke and other complication. Therefore it is important to treat asysmptomatic patients.

DRUGS USED IN HYPERTENSION

CLASSIFICATION

Diuretics

Thiazides: Hydrochlorothiazide,

Chlorthalidone, Indapamide

High ceiling: Furosemide, etc.

K+ Sparing: Spironolactone, Amiloride.

ACE inhibitors

Captopril, Enalapril, Lisinopril,

Perindopril, Ramipril, Fosinopril, etc.

Angiotensin blockers

Losartan, Candesartan, Irbesartan, Valsartan,

Telmisartan

Direct renin inhibitor

Aliskiren

Calcium channel blockers

Verapamil, Diltiazem, Nifedipine, Felodipine,

Amlodipine, Nitrendipine, Lacidipine, etc.

β Adrenergic blockers

Propranolol, Metoprolol, Atenolol, etc.

β + α Adrenergic blockers

Labetalol, Carvedilol

α Adrenergic blockers

Prazosin, Terazosin, Doxazosin

Phentolamine, Phenoxybenzamine

Central sympatholytics

Clonidine, Methyldopa

Vasodilators

Arteriolar: Hydralazine, Minoxidil,

Diazoxide

Arteriolar + venous: Sodium nitroprusside

DIURETICS

Diuretic is standard antihypertensive drugs over the past few decades. They do not lower BP in normotensives patients. Thiazides are the diuretic of choice for uncomplicated hypertension. Chlorthalidone is much longer acting than compared to hydrochlorothiazide and may have twenty four hour action. The antihypertensive mechanism of action of diuretics is:

1. First, they lowers plasma and e.c.f. volume by 5–15%, and this lead to decrease in c.o.
2. Subsequently, compensatory mechanisms operate to regain Na+ balance and plasma volume so that c.o. is restored. But the fall in BP is maintained by a slowly developing reduction in t.p.r.
3. The reduction in t.p.r. is most due to an indirect consequence of a small persisting Na+ and volume deficit. This decrease in intracellular Na+ concentration in the vascular smooth muscle may reduce stiffness of blood vessel wall, increase their compliance and inhibits responsiveness to constrictor stimuli. Similar effects are also produced by salt restriction so antihypertensive action of diuretics is lost when salt intake is high in the diet.

Thiazides have mild antihypertensive action, average fall in mean arterial pressure is less than10 mm Hg. They are effective by themselves in less than 30% cases (mostly low grade hypertension) but they potentiate all other antihypertensive drugs (except DHPs) and prevent development of tolerance to

other antihypertensive drugs. Hence, in combination, they are useful in any grade of hypertension. They are mostly used in the elderly patients and maximal antihypertensive efficacy is reached at dose of 25 mg/day.

High ceiling diuretics Furosemide, is a strong diuretic, but it as a weaker antihypertensive effect than thiazides: The explanation to this paradox may lie in its brief duration of action of furusemide. The natriuretic action of furosemide lasts only 4–6 hr after the conventional morning dose and it is followed by compensatory increase in proximal tubular reabsorption of Na+. Furosemide diuretics are more liable to cause fluid and electrolyte imbalance, weakness and other side effects. They are indicated in treatment of hypertension only when it is complicated by:

(a) Chronic renal failure were thiazides are ineffective, both as diuretic and as an antihypertensive drug.
(b) Coexisting refractory CHF.
(c) Resistance to combination antihypertensive drug regimens containing a thiazide, or marked fluid retention due to use of potent vasodilators.

Desirable properties of thiazide diuretics as antihypertensives are:

1. They can be used as a once a day dosing
2. No fluid retention, no tolerance develops.
3. They are effective in isolated systolic hypertension (ISH).
4. They reduce the risk of hip fracture in the elderly due to hypocalciuric action of thiazides and low cost.

The draw backs of diuretics are

- Hypokalaemia
- Erectile dysfunction
- Carbohydrate intolerance
- Dyslipidemia
- Hyperuricaemia
- Increased incidence of sudden cardiac death.

Consequently, prescribing of diuretics for antihypertension decreased. But over the past 25 years thiazides have been used successfully at lower doses that is (12.5–25 mg/day Hydrochlorothiazide) alone or in combination with a K+ sparing diuretic.

Findings with low dose thiazide therapy are:

- Even though serum K+ level falls a little, significant hypokalaemia does not occur.
- Continuous ECG recording studies have also failed to document increased occurrence of arrhythmias during low-dose thiazide therapy.
- Impairment of glucose tolerance or increase in serum cholesterol or hyperuricaemia over long-term are very minimal.
- Overall mortality and morbidity is very much reduced in long-term trials.
- Though they are not as effective as ACE inhibitors in reversing left ventricular hypertrophy, some recent trials in mild to moderate hypertension have found thiazides also reduce left ventricular mass.

The JNC 7 also recommends starting low-dose (12.5–25 mg) thiazide therapy, preferably with added K+ sparing diuretic, as a first choice treatment of essential hypertension, especially in the elderly. If the low dose thiazide (25 mg/day) fails to reduce blood pressure to desired level then another antihypertensive should be added, rather than increasing dose of the thiazide. Potassium sparing diuretics.

Spironolactone, eplerenone and amiloride lowers BP slightly. However, they are used only in combination with a thiazide diuretic to prevent K+ loss. They are used especially in refractory hypertension.

ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS

The ACE inhibitors are the first choice drugs in all grades of essential as well as renovascular hypertension. Most patients require lower doses, which are very well tolerated. Used alone they control hypertension in more than 50% patients.

ACE inhibitors will increase renal blood flow and retard diabetic nephropathy and regress left ventricular/vascular hypertrophy. They are the drug of choice in patients with diabetes, nephropathy and left ventricular hypertrophy, CHF, angina and post MI cases.

They are more effective in younger (< 55 year) hypertensives than in the elderly hypertensive patients. Dry persistent cough is the most common side effect.

ANGIOTENSIN RECEPTOR BLOCKER

In a dose of 50 mg/day losartan is very effective antihypertensive drug. Action starts early and reaches peak at 2–4 weeks. Addition of 12.5 mg/day hydrochlorothiazide further increase the fall in BP.

The newer ARBs— such as valsartan, candesartan, irbesartan and telmisartan have been shown to be as effective antihypertensives as ACE inhibitors. Since ARBs does not increase kinin levels cough does not occur. Angioedema, urticaria and taste disturbance are also very rare.

Several interventional endpoint reduction trials like LIFE (2002), VALUE (outcomes in hypertensive patients with valsartan or amlodipine, 2004), SCOPE (study on cognition and prognosis in the elderly; stroke prevention with candesartan in elderly with isolated systolic hypertension, 2004), JLIGHT (Japanese losartan therapy intended for global renal protection in hypertensive patients, 2004) have attested to the favorable effects of ARBs on morbidity and mortality in hypertensive patients. As antihypertensive, use of ARBs has outstripped that of ACE inhibitors.

β -ADRENERGIC BLOCKERS

Beta blockers are mild antihypertensives, they do not significantly lower BP in normotensives. Used alone they reduce only little fall in BP. Additional BP lowering can be obtained when they are combined with other drugs. The hypotensive response to β blockers will develop over 1–3 weeks.

The antihypertensive action of most β blockers is maintained over 24 h. So they can be used as single daily dose. However there are several contraindications to β blockers, including cardiac, pulmonary and peripheral vascular disease.

Because of absence of postural hypotension, bowel alteration, salt and water retention and a low incidence of side effects, and once a day regimen, β blockers are first choice drugs recommended by JNC 7 and WHO-ISH, especially for young non-obese hypertensives.

β blockers are considered less effective and less suitable for the older hypertensive. Rebound hypertension will occur on sudden discontinuation of β blockers.

β +α ADRENERGIC BLOCKERS

Labetalol is a combined α and β blocker; it reduces t.p.r. and acts faster than pure β blockers. It used as an i.v. for rapid BP reduction in hyperadrenergic states, cheese reaction, clonidine withdrawal, eclampsia, etc. Oral labetalol therapy is mainly restricted to moderately severe hypertension not responding to a pure β blocker.

Carvedilol is a nonselective β + weak selective α1 blocker that produces vasodilatation and antioxidant/free radical scavenging properties. Side effects are similar to labetalol; liver enzymes may rise in some.

α-ADRENERGIC BLOCKERS

Prazosin is a selective α1 antagonist dilates both resistance and capacitance vessels. It produces reduction in t.p.r. and mean BP along with minor decrease in venous return and c.o. However, unlike hydralazine, there is little reflex cardiac stimulation and renin release during long-term therapy. It decreases central sympathetic tone.

Renal blood flow and g.f.r. are maintained but fluid retention may attend fall in blood pressure. Cardiovascular reflexes are not impaired during chronic therapy, but postural hypotension and fainting may occur in the beginning—called ‘first dose effect’.

This may disappears with continued therapy, but may persist in the elderly patients. For this reason, prazosin is always started at low dose (0.5 mg) usually given at bedtime and gradually increased to twice daily dose till an adequate response is achieved.

An oral dose produces peak fall in BP after 4–5 hours and the effect lasts for nearly 12 hours. Alpha blockers does not impair carbohydrate metabolism and it is suitable for diabetics, but not if neuropathy is present, because postural hypotension will be accentuated.

- It as a small but favorable effect on lipid profile by lowering LDL cholesterol and triglycerides and increasing HDL.
- Additionally they give symptomatic improvement in coexisting benign prostatic hypertrophy. Apart from postural hypotension, other side effects are headache, drowsiness, dry mouth, weakness, palpitation, nasal blockade, blurred vision and rash. Ejaculation is impaired in males. Fluid retention due to prazosin monotherapy may precipitate CHF.

Prazosin is used as a moderately potent antihypertensive, but is not used as a first line antihypertensive drug because fluid retention and tolerance gradually develops with monotherapy—necessitating dose increase leading to more side effects and risk of developing CHF. It can be added to a diuretic + β blocker in those who are not achieving target BP. Terazosin, Doxazosin are long-acting congeners of prazosin with similar properties and are suitable for once daily dosing.

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers (CCBs) are another class of first line antihypertensive drugs. All 3 subgroups of CCBs, viz. dihydropyridines (DHPs, e.g. amlodipine), phenylalkylamine (verapamil) and benzothiazepine (diltiazem) are equally efficacious antihypertensives. They lower blood pressure by decreasing peripheral resistance without compromising cardiac output. Despite vasodilatation, fluid retention is insignificant.

Ankle edema that occurs in some patients on CCBs is due to increased hydrostatic pressure across capillaries of the dependent parts as a result of reflex constriction of post capillary vessels in these vascular beds. The onset of antihypertensive action of CCBs is quick.

With the availability of long acting preparations, these drugs can be administered once a day dose. Monotherapy with CCBs is effective in 50% hypertensives; their action is independent of patient's renin status, and they may improve arterial compliance. Other advantages of CCBs are:

1. No impairment of physical work capacity.
2. No sedation or other CNS effects, cerebral perfusion is maintained.
3. Not contraindicated in asthma, angina (especially variant) and PVD patients and may benefit these conditions.
4. Do not impair renal perfusion.
5. Do not affect male sexual function.
6. No deleterious effect on plasma lipid profile, uric acid level and electrolyte balance.
7. Shown to have no/minimal effect on quality of life.
8. No adverse fetal effects and can be used during pregnancy (but can weaken uterine contractions during labour).

The CCBs do not decrease venous return. DHPs may even increase it and jeopardize hemodynamic in patients with diastolic dysfunction. DHPs (especially short-acting) also tend to increase HR and c.o. by invoking reflex sympathetic stimulation.

The increased mortality among coronary heart disease patients has been due to repeated surges of adrenergic discharge and marked swings of blood pressure attending each dose of rapidly acting DHP. However, this risk can be overcome with slow acting DHPs.

The Hypertension optimal treatment (HOT), and Swedish trial in old patients with hypertension-2 (STOP- 2) studies have also found CCBs equi-effective as diuretics/ β blockers/ACE inhibitors in reducing cardiovascular/total mortality. On the other hand, CCBs do not afford survival benefit in post MI patients as β blockers, ACE inhibitors or low dose thiazides do.

CCBs are also not as effective in suppressing left ventricular hypertrophy as ACE inhibitors. But still CCBs continue to be used as one of the first line monotherapy options because of their high efficacy and excellent tolerability. They are preferred in the elderly hypertensive. The long-acting DHPs are next to ACE inhibitors in reducing albuminuria and slowing disease progression in hypertensive/ diabetic nephropathy.

Use of rapid acting oral nifedipine for urgent BP lowering in hypertensive emergencies is out dated. In fact, there is currently no therapeutic indication for rapid and short-acting oral DHPs in hypertension. Other concerns in the use of CCBs as antihypertensive are:

(i) The negative inotropic/dromotropic action of verapamil/diltiazem may worsen CHF and cardiac conduction defects (DHPs are less likely to do so).

(ii) By their smooth muscle relaxant action, the DHPs can worsen gastroesophageal reflux.

(iii) CCBs (especially DHPs) may accentuate bladder voiding difficulty in elderly males.

TREATMENT OF HYPERTENSION

The aim of antihypertensive therapy is to prevent morbidity and mortality associated with persistently raised BP by lowering it to an acceptable level, with minimum inconvenience to the patient. Both systolic and diastolic BP predicts the likelihood of target organ damage (TOD) and complications such as:

a) Cerebrovascular disease, transient ischaemic attacks, stroke, ncephalopathy.
b) Hypertensive heart disease - left ventricular hypertrophy, CHF.
c) Coronary artery disease, angina, myocardial infarction, sudden cardiac death.

d) Arteriosclerotic peripheral vascular disease, retinopathy.

e) Dissecting aneurysm of aorta.

f) Glomerulopathy, renal failure.

Patients who have already suffered from TOD have greater risk of further organ damage and death at any level of raised BP, than those without TOD. Since the risk of complications depends not only on the level of BP, but also on other risk factors and existing TOD, these have also to be considered in deciding when to start drug therapy, as well as in selection of drugs and in devising therapeutic regimens.

Beneficial effects of lowering BP have been established in all patients having BP above 140/90 mm Hg. In hypertensives having diabetics, lowering diastolic BP to 80 mmHg was found to reduce cardiovascular events more than reducing it upto 90 mm Hg.

If the cause of hypertension can be identified such as hormonal, vascular abnormality, tumour, renal disease, drugs etc then all efforts should be made to remove cause. First nonpharmacological measures such as life style modification, Na+ restriction, aerobic activity or exercise, weight reduction, moderation in alcohol intake, mental relaxation, etc should be tried along with antihypertensive drugs.

The level to which BP should be lowered is not clear. But a value of < 140 systolic and < 90 mmHg diastolic is considered adequate response to therapy,

because it clearly reduces morbidity and mortality. In patients with CAD, heart failure, stroke, etc it should be even reduced to 120/80.

Efficacy wise all the 4 classes of drugs are equal . But the drug for initial therapy is selected on the basis of suitability criteria taking into consideration of the patients age, life style issues, risk factors, concomitant medical conditions, tolerability in respect of the individual patient and cost of different drugs.

The general principles of antihypertensive therapy enunciated in JNC7, WHO-ISH and British Hypertension Society* (BHS) 2004, guidelines may be summarized as:

1. Except for stage II hypertension, start with a single drug, which for majority of patients it will be thiazide. However, an ACE inhibitor/ARB or CCB or in some cases β blocker may also be considered.
2. The BHS (2004) recommended following the A B C D rule (A—ACE inhibitor/ARB; B—β blocker; C—CCB, D—diuretic). While A and (in some cases) B are preferred in younger patients (<55 years), C and D are preferred in the older older patients (> 55 years).
3. Start therapy at low dose and then if needed increase dose moderately. Thiazide dose should not be more than 12.5–25 mg/day.
4. If no response then change to a drug from another class, or low dose combination from other classes.
5. If side effect to the initially chosen drug occurs then either substitute with drug of another class or reduce dose and add a drug from another class.

6. Majority of stage II hypertensives are started on a 2 drug combination and one of which usually is a thiazide diuretic.

With the above approach 50–70% stage I hypertensives can be successfully treated, at least initially, with monodrug therapy. Combination therapy Though JNC 7, WHOISH and BHS guidelines emphasize on single drug therapy and the addition of a second (and third or even fourth) drug is also highlighted when monotherapy fails.

Since BP is kept up by several interrelated factors, an attempt to block one of them tends to increase compensatory activity of the others. So it is rational in such cases to combine drugs with different mechanisms of action or different patterns of hemodynamic effects:

a) Drugs which increase plasma renin activity— diuretics, vasodilators, CCBs, ACE inhibitors may be combined with drugs which lower plasma renin activity—β blockers, clonidine, methyldopa.

b) All sympathetic inhibitors (except β blockers) and vasodilators, except CCBs, cause fluid retention leading to tolerance. Addition of a diuretic checks fluid retention and development of tolerance.

c) Hydralazine and DHPs cause tachycardia which is counteracted by β blockers, while the initial increase in t.p.r. caused by nonselective β blockers is counteracted by the vasodilator.

d) ACE inhibitors/ARBs are particularly synergistic with diuretics; this combination is very good for patients with associated CHF or left ventricular hypertrophy.

e) In step 2 when two drugs are to be used, the BHS recommend combining one out of A or B with one out of C or D.

f) Use of combined formulation improves compliance and usually lowers cost.

g) In the step 3 (when two drugs are inadequate in achieving target BP lowering), triple drug regimen is prescribed. Both C and D are combined with A or B, whereby large majority of patients are adequately controlled.

h) Patients who fail to reach the goal BP despite being adherent to full doses of an appropriate 3 drug (including a diuretic) regimen have been labeled by JNC7 as 'resistant hypertension'. In them even 4 drug therapy step 4 may have to be given to achieve the target BP. However, the patient must be reevaluated and factors like non-compliance, pseudo tolerance, need for a loop diuretic, drug interactions, secondary hypertension, etc. must be first excluded. All four first line drugs are used together, or an α1 blocker is included with 3 first line drugs. Eplerenone also is being used as the 4th drug now. Hydralazine or clonidine are rarely included.

Combinations to be avoided

1. An α or β adrenergic blocker with clonidine: apparent antagonism of clonidine action has been observed.
2. Hydralazine with a DHP or prazosin; because of similar pattern of hemodynamic action.
3. Verapamil or diltiazem with β blocker, because marked bradycardia, A-V block can occur.
4. Methyldopa with clonidine or any two drugs of the same class.

When the BP has been well controlled for > 1 year, stepwise reduction in dose and/or withdrawal of one or more components of a combination may be attempted to work out a minimal regimen that will maintain the target BP. However, in most patients of essential hypertension, drug therapy is usually life-long.

Hypertension in pregnancy

A sustained BP reading above 140/90 mm Hg during pregnancy has delirious effect on both mother and the foetus therefore reduction of BP clearly reduces risks

Two types of situations are possible:

a) A woman with preexisting essential hypertension becomes pregnant.
b) Pregnancy induced hypertension; as in toxaemia of pregnancy—preeclampsia.

Toxaemic hypertension is associated with a hyperadrenergic state, decrease in plasma volume (despite edema) and increase in vascular resistance. In the first category the same therapy instituted before pregnancy may be continued.

Antihypertensives to be avoided during pregnancy

ACE inhibitors, ARBs will produce Risk fetal damage, growth retardation. Diuretics drugs tend to reduce blood volume and worsen uteroplacental perfusion deficit (of toxaemia)—increase risk of fetal wastage, placental infarcts, miscarriage, stillbirth.

Nonselective β blockers, Propranolol has been implemented to cause low birth weight, decreased placental size, neonatal bradycardia and hypoglycaemia.

Sod. Nitroprusside is contraindicated in eclampsia. Antihypertensives found safer during pregnancy are labetalol and Methyldopa. Dihydropyridine CCBs if used, should be discontinued before labour as they weaken uterine contractions.

Hypertensive emergencies and urgencies

Systolic BP > 220 or diastolic BP > 120 mm Hg with evidence of active end organ damage is labelled ‘hypertensive emergency’, while the same elevation of BP without overt signs of end organ damage is termed ‘hypertensive urgency’. Severity and rate of progress of TOD determines the seriousness of the condition.

Controlled reduction of BP over minutes (in emergencies) or hours (in urgencies) is required to counter threat to organ function and life in:

1. Cerebrovascular accident (hemorrhage) or head injury with high BP.
2. Hypertensive encephalopathy.
3. Hypertensive acute LVF and pulmonary edema.
4. Unstable angina or MI with raised BP.
5. Dissecting aortic aneurysm.
6. Acute renal failure with raised BP.
7. Eclampsia.
8. Hypertensive episodes in pheochromocytoma, cheese reaction or clonidine withdrawal.

Oral therapy

Some rapidly acting oral hypotensive drugs have been used in hypertensive urgencies, but now they are considered neither necessary nor safe.

Nifedipine (10 mg soft geletine cap.) orally or s.c. every 30 min was widely employed in urgencies. This practice has now been abandoned because it often causes abrupt fall in BP and precipitates MI or stroke, or may be fatal. Once the drug is ingested, rate and degree of fall in BP cannot be controlled, and adverse consequences outweigh its advantages.

Captopril (25 mg oral every 1–2 hours) was also used, but response is variable and it carries risk of excessive hypotension.

Clonidine (100 μg every 1–2 hours oral) acts mostly in 30–60 min, but produces sedation and rebound rise in BP on stopping the drug.

Parenteral therapy

Parenteral (preferably i.v.) drugs with controllable action are used both in emergencies and in urgencies (less vigorously in the latter). However, many studies consider that in the absence of end organ damage (urgencies), i.v drugs are not necessary. But slow reduction of BP with oral drugs is adequate and safer.

Mean BP should be lowered by no more than 25% over a period of minutes or a few hours and then gradually to not lower than 160/100 mm Hg.

Drugs employed are:

1. Sodium nitroprusside because of its predictable, instantaneous, titratable and balanced arteriovenous vasodilatory action. Nitroprusside (20–300 μg/min) is the drug of choice for most hypertensive emergencies. However, it is toxic in high dose and when used for longer period of time. GTN may be better choice when there is associated MI or LVF. In aortic dissection, nitroprusside as to given with esmolol infusion. Another limitation with nitroprusside is that it needs an infusion pump and constant monitoring.

2. Glyceryl trinitrate when given by i.v. infusion (5–20 μg/min) acts within 2–5 min and has brief titratable action, but it is a less potent hypotensive. Its predominant venodilator action makes it particularly suitable for lowering BP after cardiac surgery and in acute LVF, MI, unstable angina, but not in other

conditions. Disadvantage is tolerance starts developing after 18–24 hours of continuous infusion.

3. Hydralazine 10–20 mg i.m. or slow i.v. injection acts within 20–30 min and keeps BP low for 4–8 hours, but is less predictable, and not a first line drug. It has been especially used in eclampsia. It produces tachycardia and should be avoided in patients with myocardial ischaemia or aortic dissection.

4. Esmolol this β blocker given as 0.5 mg/kg bolus followed by slow i.v. injection (50–100 μg/kg/min) acts within 1–2 min and action lasts for 10–20 min. It is useful when cardiac contractility and work is to be reduced, such as in aortic dissection.

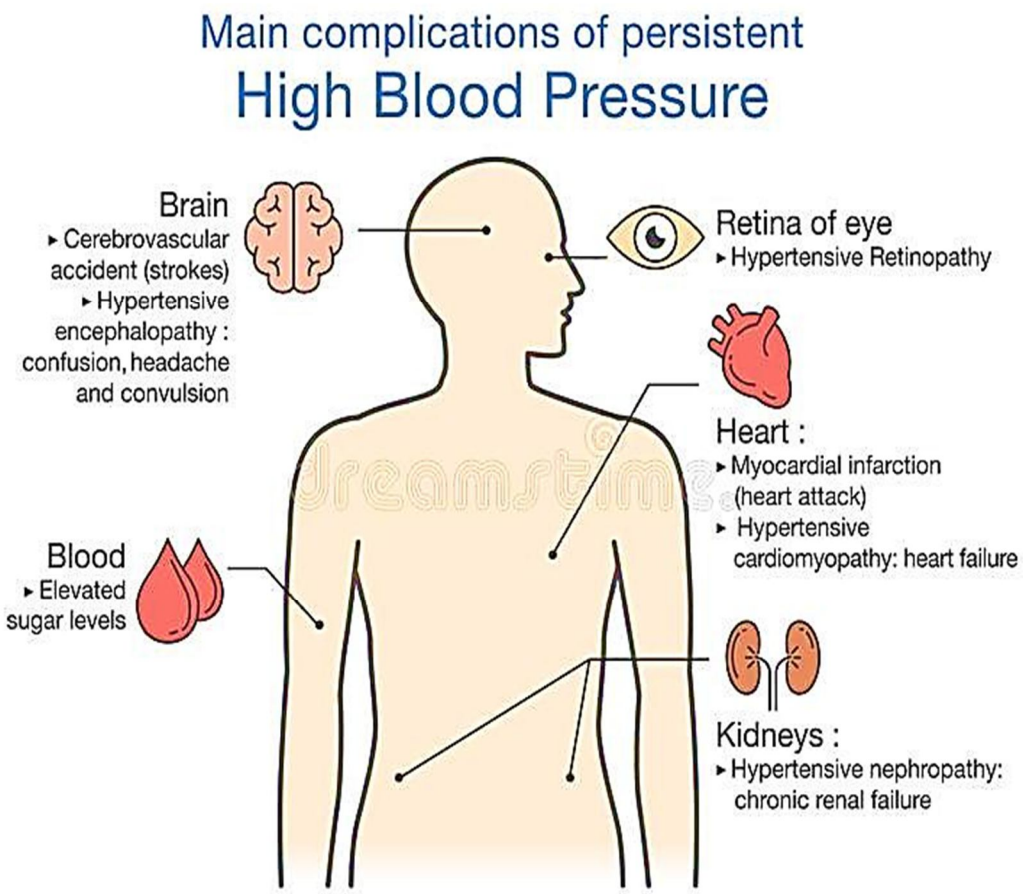
   Nitroprusside is given concurrently, because the BP lowering action of Esmolol is weak. It is a useful hypotensive and bradycardiac drug during and after anesthesia. Excess bradycardia is to be guarded.

5. Phentolamine this nonselective α1 + α2 blocker is the drug of choice for hyperadrenergic states, e.g. hypertensive episodes in pheochromocytoma, cheese reaction or clonidine withdrawal. Injected i.v. (5–10 mg) it acts with in 2 min and action lasts for 5–15 min. Tachycardia and myocardial ischaemia may complicate its use. A β blocker may be added along with this.

6. Labetalol Injected i.v. is an alternative to an α blocker + a β blocker combination for lowering BP in pheochromocytoma, etc. but has only weak α blocking action. It has been used to lower BP in MI, unstable angina,

eclampsia as well. It is also good for patients with altered consciousness, because it does not cause sedation or increase intracranial pressure. Concomitant CHF or asthma are contraindication for its use its use.

7. Furosemide (20–80 mg oral or i.v.) can be be given as an adjunct with any of the above drugs if there is volume overload (acute LVF, pulmonary edema, CHF) or cerebral edema (in encephalopathy), but should be avoided when patient is in hypovolemic due to pressure induced natriuresis (especially in eclampsia, pheochromocytoma).



RESVERATROL

Introduction

Resveratrol (RES) is a non-flavonoid polyphenolic compound derived from stilbene. It is a phytoalexin produced by plants, and is present more in grapes and red wine. It has a potential protective role against CVDs, and be involved in the "French paradox" characterized by the low incidence of CVDs in the French population in spite of taking high intake of saturated fats, along with moderate red wine consumption.

Therapeutic benefits of moderate red wine consumption have been shown by numerous studies to decrease blood pressure. Resveratrol is found in red grapes seeds and in plants that can survive harsh environmental condition. EFSA has categorized RESV as food supplement so it can be taken without a doctor's prescription or recommendation.

Resveratrol has a cardioprotection, antidiabetic and neuroprotective effects due to its antioxidant properties. Inaddition resveratrol has vasoprotective properties. RES has a protective action on the vascular walls against oxidation, inflammation, platelet oxidation and thrombus formation.

In vitro, cardioprotective mechanisms of RESV are due to its ability to up regulate eNOS. Which in turn shown to improve endothelial function, by improving the bioavailability of nitric oxide (NO).

Anti-Atherosclerotic Effects of RES

Atherosclerosis predominantly affects the intimal layer of the arterial vessel wall. Atherosclerosis is characterized by the deposition of extracellular lipids, and a chronic inflammation. It further leads to luminal narrowing and/or thrombus formation, which in turn leads to coronary artery disease, peripheral arterial disease or stroke.

Some preclinical studies have shown that RES could alter lipid profile by decreasing plasma triglyceride and LDL-cholesterol levels, and by increasing HDL- cholesterol.

Anti-Hypertensive Effects of RES

Hypertension is a major risk factor for CVDs. RES Anti-hypertensive effects have been demonstrated in several animal models of hypertension, after treatment by 10 to 320 mg RES/kg body weight/day, for 14 days to 10 weeks.

Many studies shown that relatively low doses of RES (5–10 mg/kg/day) significantly decreased blood pressure in animal models having hypertension along with insulin resistance. This suggests that RES would be more effective in patients with diabetes or metabolic syndrome.

Dolinsky et al. observed that a high dose of RES decreased high pressure and prevented cardiac hypertrophy in two hypertensive animal models namely spontaneously hypertensive rats and angiotensin-II infused mice. A some studies also proved RES as the ability to reverse cardiac hypertrophy and contractile dysfunction, which is associated with hypertension.

In a recent study it was found that, RES alone is ineffective in reducing blood pressure in 28 weeks old spontaneously hypertensive rats, but when given in a combination of RES with amlodipine (a blood pressure lowering agent) it was more effective than amlodipine monotherapy alone in improving cardiovascular parameters.

The mechanisms involved in the antihypertensive properties of RES are endothelium-dependent, with the activation of AMPK (a regulator of energy metabolism), SIRT-1 and Nrf2. Which results in a vasodilatation due to improved availability of NO, in relation to increased expression and activity of eNOS.

Endothelium-independent vasodilatation mechanisms also been reported, such as activation of AMPK activation, leading to an inhibition of angiotensin II (AngII)-induced phosphorylation of myosin phosphatase-targeting subunit 1 and myosin light chain leading to inhibition of vascular smooth muscle contractility .

Therefore daily treatment with RES decreased hypertension in an experimental model of AngII-induced hypertensive mice. The decrease in blood pressure is often leads to improvement of metabolic parameters.

Resveratrol when added to a standard anti-hypertensive therapy will control blood pressure by increasing the production of Nitric Oxide (NO1 an endogenous and potent vasodilator). Endothelium lining blood vessels will produce NO, which facilitates vasodilatation by activating the enzyme guanylate cycloxygenase (GC). GC then initiates a signaling cascade, which results in relaxation of the smooth muscle layer of blood vessels and produce vasodilatation. This vasodilatation reduces peripheral resistance which directly affects arterial pressure and lowers blood pressure.

Resveratrol has been reported to have a dose – dependent anti-hypertensive effect in various animal models of systemic hypertension. Resveratrol at a low dose of 2.5mg/kg body weight/day has been shown to enhance the effects of other anti-hypertensive medication in the spontaneously hypertensive rat models.

Additionally, resveratrol protects against and or reverse pulmonary hypertension in rat. It is also effective in preventing high fat induced and high sucrose induced arterial stiffness in non human primates. Resveratrol mediated reduction in hypertension has been attributed to various mechanism including improvement in oxidative stress, inflammation, endothelial dysfunction and vasodilatation.

Resveratrol have a incremental effect in lowering high BP when taken along with the standard anti-hypertensive medication. Resveratrol reduce the dosage of anti-hypertensive medication that has side effects.

Relatively low doses of resveratrol (5-10mg /kg/day) were sufficient to lower BP in hypertension animal models associated with Insulin resistance, suggesting that resveratrol may be more effective in lowering BP in patients with diabetic or metabolic syndrome.

In another study resveratrol reduced systolic BP in obese rats. Likewise resveratrol treatment (20mg/kg/day) significantly lowered systolic and diastolic BP's in female rats fed with high fat diet, but not in rats fed with normal chew diet.

Since age, diabetes and obesity are important risk factors for endothelial dysfunction. Resveratrol will prevent both obesity related and age related declines in endothelial function. Resveratrol also suppressed basal superoxide production and lipid peroxide levels in the diabetic rats thereby protecting the endothelial integrity from diabetes.

Overall resveratrol protection effect on the vasculature may play an important role in the prevention of hypertension and / or in the protection against hypertension induced end organ damage in the long term.

In addition to systemic hypertension resveratrol also shown to decrease pulmonary hypertension in some animal studies. Resveratrol improve endothelial function, attenuate inflammation and oxidative stress and inhibit proliferation of pulmonary artery smooth muscle cells in the models.

In addition, resveratrol has shown to reverse established pulmonary hypertension when it was administered 28 days after monocrotaline injection. These studies show that resveratrol has multiple beneficial effects on the vasculature and may hold promise for the treatment and / or prevention of systemic hypertension as well as pulmonary hypertension.

Aim & Objectives

AIMS & OBJECTIVES

AIM :

To evaluate the efficacy and tolerability of Resveratrol as an add on therapy to standard treatment in patient with systemic hypertension.

OBJECTIVES:

Primary Objective:

- To observe the reduction in systolic and diastolic blood pressure.

Secondary Objective:

- To observe for any adverse effect with the study drug.

Methodology

METHODOLOGY

The study was undertaken in mild to moderate hypertensive patients to find out the efficacy and tolerability of resveratrol as an add on therapy to the standard anti-hypertensive regimen in the reduction of blood pressure.

The study was conducted in institute of pharmacology, madras medical college, Chennai in collaboration with department of Internal medicine, Rajiv Gandhi Government General Hospital, Chennai.

STUDY DESIGN:

This study was an open-label, randomized, comparative, prospective, parallel group study.

STUDY CENTRE:

- Hypertension Clinic,

  Department of Internal Medicine,

  Madras Medical College &

  Rajiv Gandhi Government General Hospital, Chennai.

STUDY PERIOD:

The study was carried out from November 2016 to December 2017.

STUDY DURATION:

4 weeks for each patient.

STUDY POPULATION:

Patient attending the Outpatient department of Hypertension clinic, Department of Internal Medicine, Rajiv Gandhi Government General Hospital, Chennai

SAMPLE SIZE:

60 patients (30 patients in each group)

STUDY PROCEDURE:

Inclusion criteria:

- Patients of either sex
- Patients in the age group of 18-65 years
- Patients with mild to moderate hypertension

  (Mild hypertension: systolic blood pressure 140-159 mm Hg and diastolic blood pressure 90-99 mm Hg, Moderate hypertension : systolic blood pressure 160-179 mm Hg and diastolic blood pressure 100-109mm Hg)
- Patients with Body Mass Index (BMI) of 18-25
- Patients willing to give written informed consent

Exclusion criteria:

- Patients with history of septic arthritis, meningitis, pneumonia
- Patients with history of pyelonephritis, tonsillitis, otitis media
- Patients with upper respiratory tract infection
- Patients with any other active infection
- Patients with any history of surgery in the recent past 3 months
- Patients with history of malignancies
- Patients with history of myocardial infraction
- Patients with evidence of gastrointestinal tract, renal, endocrine, cardiovascular abnormalities and any other major systemic illness
- Pregnant and Lactating women
- Patients who cannot comply with the protocol
- Patients not willing to give written informed consent

The study commenced after obtaining approval from the Institutional Ethical Committee.

ENROLLMENT VISIT:

Patients who attended the Outpatient department of Hypertension Clinic, Department of Internal Medicine, Rajiv Gandhi Government General Hospital, Chennai were explained in detail about the study procedure, purpose and its benefits.

They were explained about the following:

The purpose of this study was to

- Achieve better blood pressure reduction
- Reduce complications
- Improve the quality of life in hypertensive patients

Written informed consent was obtained from patients willing to participate in the study, in the prescribed format in the regional language prior to the performance of the study procedures. If the patient is illiterate, left thumb impression was sought. This was done in the presence of impartial witness. Patients advised to come on next day at 8.00A.M on empty stomach for screening procedure.

SCREENING (Visit 0):

Patients who gave written informed consent for participation in the study were screened by detailed medical history, blood pressure monitoring, physical and systemic examination, baseline demographic characteristics were recorded. Blood was drawn for determining the hematological and serum biochemical tests. 97 patients were screened.

LABORATORY INVESTIGATIONS:

The following laboratory investigations were done at screening

1. **Complete Hemogram**
    a. Hemoglobin
    b. Total WBC count
    c. Neutrophil count
    d. Lymphocyte count
    e. Red Blood Cell count.
2. **Blood Biochemistry**
    a. Blood sugar
    b. Blood urea
    c. Serum creatinine
3. **Urine Analysis**
4. **ECG**

RECRUITMENT AND GROUPING:

Among 97 patients screened, 60 patients who fulfilled the inclusion and exclusion criteria were recruited for the study. The recruited 60 patients were randomized into two groups consisting of 30 patients.

GROUPING:

- **CONTROL GROUP :** Amlodipine 5mg OD
- **TEST GROUP :** Amlodipine 5mg + Cap. Resveratrol 100mg OD

STUDY VISITS:

- **VISIT 1 (Base line) :**
- Out of 97 patients screened 60 patients with systolic blood pressure in the range of 140-179 mmHg and diastolic blood pressure in the range of 90-109 mmHg were recruited for the study. The following procedure were done at visit I.

Randomization:

- Randomization into two groups
  - Each group consisting of 30 patients
  - Control group patients were given Amlodipine 5mg OD
  - Test group patients were given Amlodipine 5mg and Resveratrol 100mg 0D
  - Patients were given medication for four weeks
  - Instructed to come fortnightly to collect the medication
  - Patients were instructed to bring the empty foils at the end of 2 weeks to check the patients compliance
  - Patients blood pressure was recoded
  - Detailed medical history and clinical examination was done
  - Patients were advised to report to the investigator as soon as possible in case of occurrence of any adverse effects

Patients were instructed to report to the investigator in case of occurrence of any other illness and intake of other medications for the same.

VISIT 2 (At the End of 2nd week):

- Patients compliance was checked.
- Patients blood pressure was recorded.
- Detailed medical history and clinical examination were done.
- Blood samples were collected for the routine hematological and biochemical parameters.
- Medications were issued to the patients for 2 weeks.
- Instructed to come fortnightly to collect the medication.
- Patients were advised to report to the investigator as soon as possible in case of any adverse effects.
- Patients were instructed to report to the investigator in case of occurrence of any other illness and intake of other medications for the same.

VISIT 4 (At the End of 4 weeks) :

- Patients blood pressure were recorded.
- Detailed medical history and clinical examination were done.
- Blood samples were collected for the routine hematological and biochemical parameters.
- Instructed to come fortnightly to collect the medication for 2 weeks.

- Patients were instructed to bring the empty foils at the end of 2 weeks to check the patients compliance.
- Patients were advised to report to the investigator as soon as possible in case of occurrence of any adverse effects.
- Patients were instructed to report to the investigator in case of occurrence of any other illness and intake of other medications for the same.
- Patients were instructed to attend the Out Patient department of Hypertension clinic to get the medications regularly.

This study was undertaken to find out the efficacy and tolerability of resveratrol as an add on therapy to the standard anti hypertensive in the reduction of blood pressure in the patients with mild to moderate hypertension.

RESULTS

Out of 97 patients screened, 60 patients who fulfilled the inclusion and exclusion criteria were recruited for the study. They were randomized into two groups, Group I and Group II, each consisting of 30 patients.

Group I received standard anti hypertensive treatment amlodipine 5mg OD, Group II received resveratrol100mg OD along with amlodipine 5mg OD, for a period of one month for each patient.

Parameters were assessed at the baseline, at the end of 2^{nd} week, and at the end of 4^{th} week of study. 60 patients (30 in Group I and 30 in Group II completed the study.

STATICAL ANALYSIS:

Statistical analysis was done using one way anova for comparison between groups and bonferonni's test for multiple comparison. Analysis of adverse events was done using Chi – Square test.

Reason for Drop Outs:

1. In Group I , one patient didn't turn up after 2 week of study and the remaining one patient not willing to continue the study after 3 week
2. In Group II, two patients didn't turn up after 2 week of study commencement and one patient was not willing to continue in the study after 2 week.

Results

RESULTS

TABLE 1: MEAN AGE DISTRIBUTION

GROUP	NO OF PATIENTS	MEAN AGE	SD
CONTROL	30	59.73	9.06
STUDY	30	61.03	8.81
p Value	0.5755		

Table 1 shows the mean age distribution of both the groups.

Mean age was similar in both the groups.

There were no statistically significant differences between the groups.

FIGURE 1: MEAN AGE DISTRIBUTION

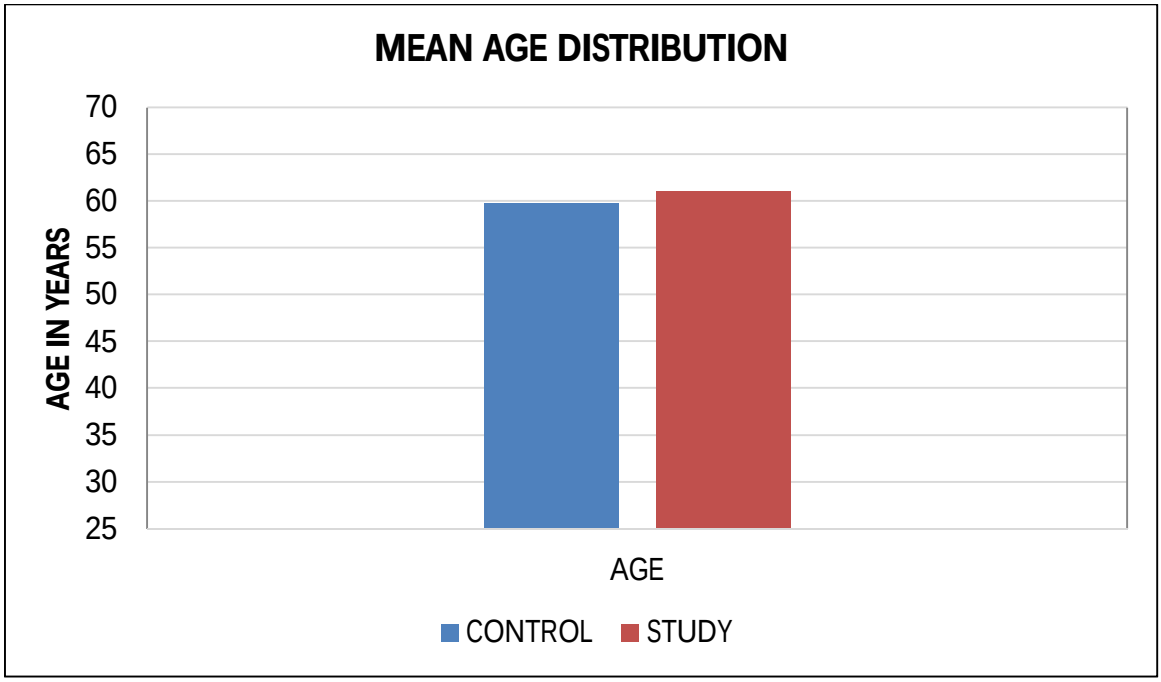


Figure 1 is the graphical representation of Table 1.

TABLE 2: AGE DISTRIBUTION

AGE IN YEARS	CONTROL GROUP		STUDY GROUP	
	NO	PERCENTAGE	NO	PERCENTAGE
45-55	10	33.33%	8	26.66%
55-65	12	40%	13	43.33%
65-75	8	26.66%	9	30%
TOTAL	30	100%	30	100%

Table 2 shows age distribution of both the groups.

Age group 55-65 had most number of patients in both the groups.

FIGURE 2: AGE DISTRIBUTION

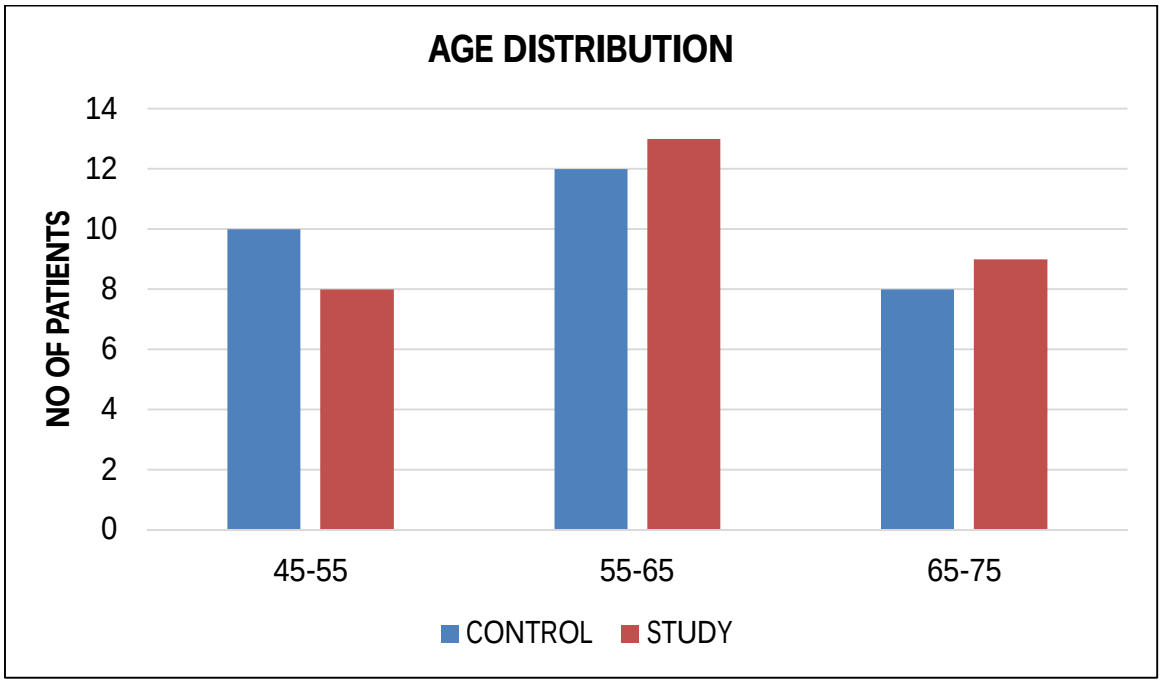


Figure 2 is the graphical representation of table 2.

TABLE 3: SEX DISTRIBUTION

	CONTROL GROUP		STUDY GROUP	
	NO OF PATIENTS	PERCENTAGE	NO OF PATIENTS	PERCENTAGE
MALE	14	46.66%	15	50%
FEMALE	16	53.33%	15	50%
TOTAL	30	100	30	100
p VALUE	0.7961			

Table 3 shows the sex distribution in both the groups.

Control group had 46.66% males and 53.33% females while study group had 50% males and 50% females.

There was no significant difference in male and female distribution in both the groups(p value=0.7961).

FIGURE 3: SEX DISTRIBUTION

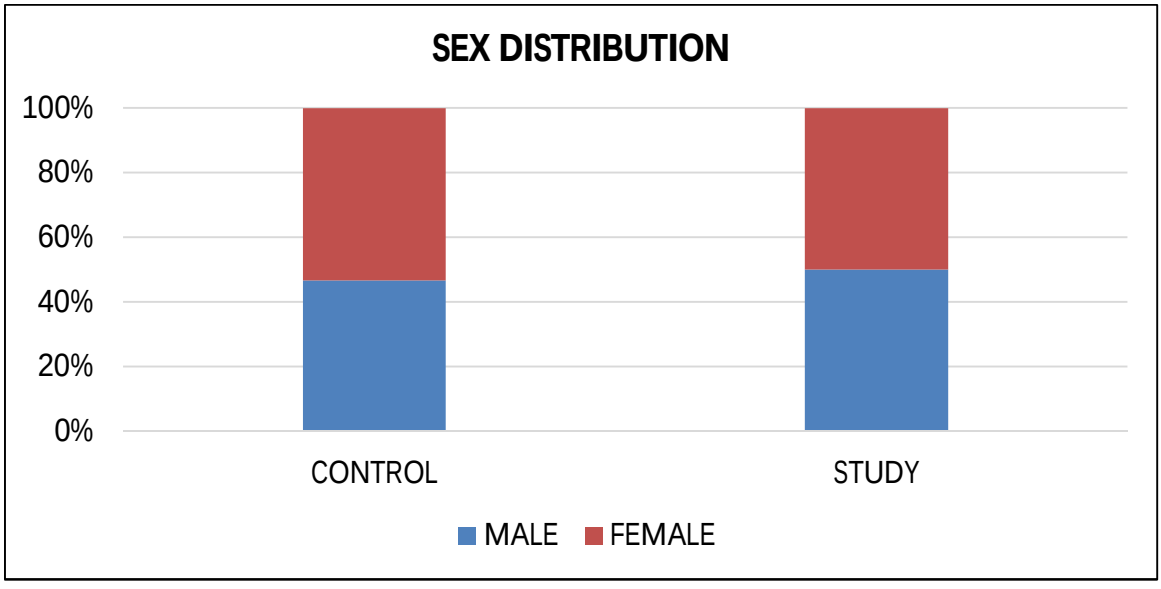


Figure 3 is the graphical representation of Table 3.

TABLE 4: SYSTOLIC BLOOD PRESSURE

GROUP	BASELINE MEAN±SD	4 WEEKS MEAN±SD	p Value
CONTROL	150.27±4.53	144.9±4.23	0.0001
STUDY	151.7±3.74	141.47±3.84	0.0001
p Value	0.1869	0.0017	

Table 4 shows the improvement systolic blood pressure in control and study group. Within group analysis showed significant improvement in systolic blood pressure both groups at 4 weeks compared to baseline (p value=0.0001).

Between the groups analysis showed a significant difference at the end of 4 weeks p value=0.0017

FIGURE 4: SYSTOLIC BLOOD PRESSURE

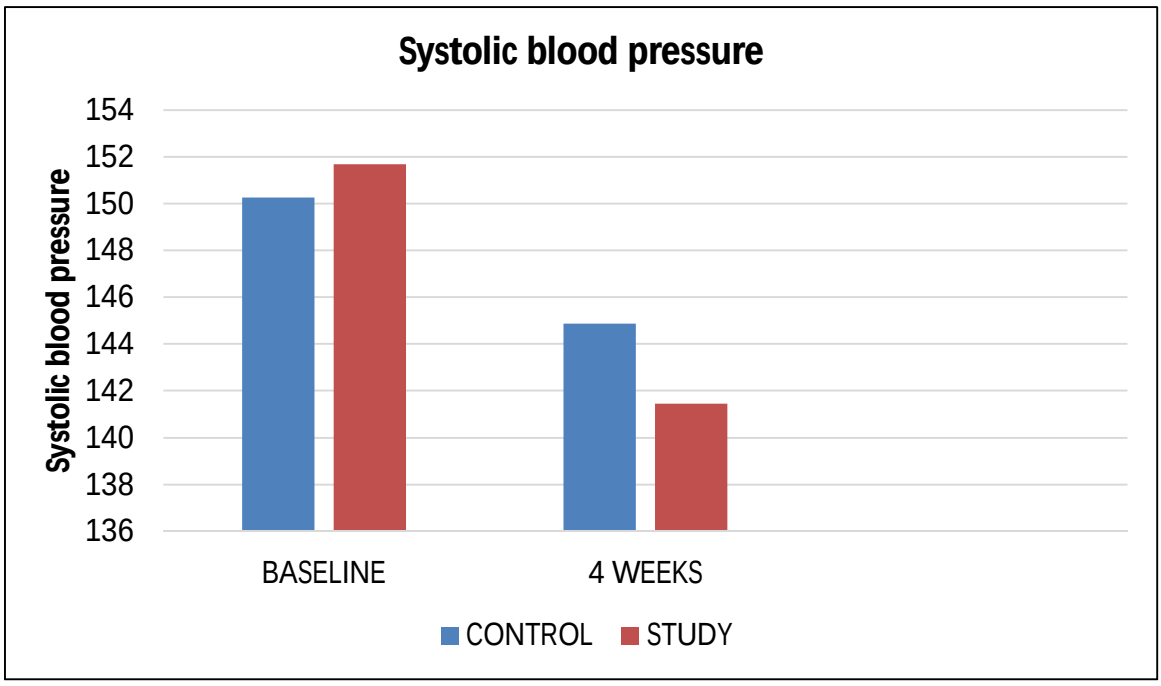


Figure 4 is the graphical representation of Table 4.

TABLE 5: DIASTOLIC BLOOD PRESSURE

GROUP	BASELINE MEAN±SD	4 WEEKS MEAN±SD	p Value
CONTROL	94.36±1.69	85.33±3.46	0.0001
STUDY	93.8±1.91	83.2±3.81	0.0001
p value	0.2299	0.0272	

Table 5 shows the improvement in diastolic blood pressure in control and study group. Within group analysis showed significant improvement in diastolic blood pressure in both groups at 4 weeks compared to baseline (p value=0.0001).

Between the groups analysis showed a significant difference at the end of 4 weeks p value=0.0272.

FIGURE 5: DIASTOLIC BLOOD PRESSURE

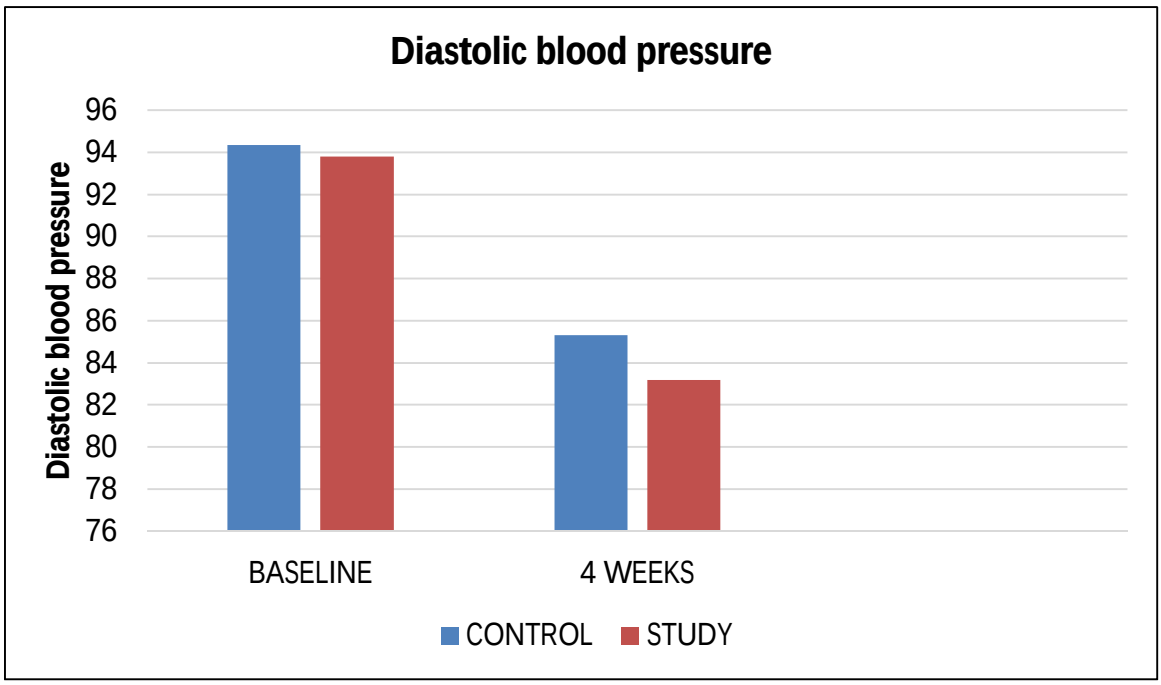


Figure 5 is the graphical representation of Table 5.

BIOCHEMICAL INVESTIGATIONS

TABLE 6: CONTROL GROUP

INVESTIGATION	BASELINE	4 WEEKS	p VALUE
RANDOM BLOOD SUGAR	134.6±6.23	132.23±6.36	0.0828
UREA	27.5±1.8	26.86±1.67	0.0598
CREATININE	0.79±0.07	0.80±0.11	0.3183

Table 6 shows the biochemical parameters of control group.

Statistical analysis within the group did not show any significant difference in random blood sugar, urea and creatinine.

TABLE 7: STUDY GROUP

INVESTIGATION	BASELINE	4 WEEKS	p VALUE
RANDOM BLOOD SUGAR	133.4±6.23	130±7.57	0.0019
UREA	27.16±1.44	27.06±1.36	0.639
CREATININE	0.79±0.07	0.80±0.09	0.3601

Table 7 shows the biochemical parameters of study group.

Statistical analysis within the group showed significant difference in random blood sugar (p =0.0019).

Statistical analysis within the group did not show any significant difference in urea, creatinine.

TABLE 8: INCIDENCE OF ADVERSE DRUG REACTIONS

	CONTROL GROUP	STUDY GROUP
NO OF ADRs	7	5

Table 8 shows the incidence of ADRs in patients of both the groups.

7 ADRs were reported in control group and 5 ADR were reported in study group.

FIGURE 6: INCIDENCE OF ADVERSE DRUG REACTIONS

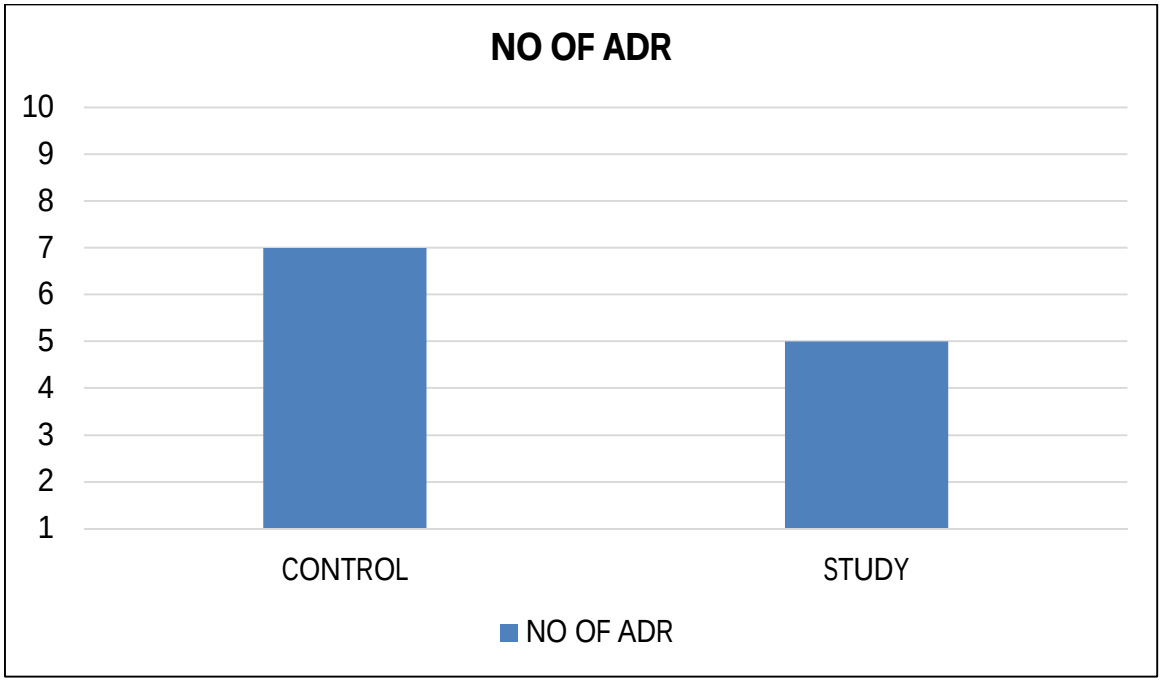


Figure 6 is the graphical representation of Table 8.

TABLE 9: ADVERSE DRUG REACTIONS MONITORING

ADR	CONTROL GROUP	STUDY GROUP
NAUSEA	1	1
GASTRITIS	1	2
MYALGIA	3	-
PALPITATION	1	-
PEDAL EDEMA	1	1
HEADACHE	-	1

Table 9 shows the adverse effect profile of both the groups.

Adverse effects were reported more in control group than in study group.

Gastritis and myalgia were the most common ADRs.

FIGURE 7: ADVERSE DRUG REACTIONS MONITORING

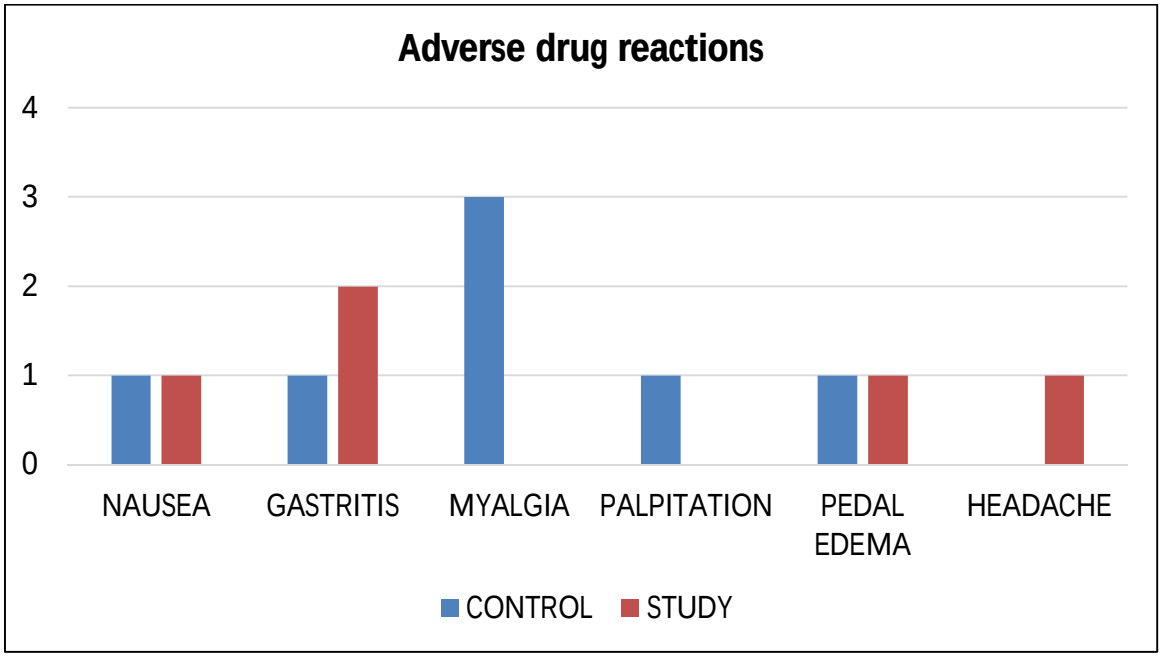


Figure 7 is the graphical representation of Table 9.

TABLE 10: CAUSALITY ASSESSMENT OF ADVERSE DRUG REACTIONS- CONTROL GROUP

ADR	Certain	Probable	Possible	Un-likely	Un-classified	Un-classifiable
NAUSEA	-	-	1	-	-	-
GASTRITIS	-	-	1	-	-	-
MYALGIA	-	-	3	-	-	-
PALPITATION	-	-	1	-	-	-
PEDAL EDEMA	-	1	-	-	-	-
HEADACHE	-	-	-	-	-	-

Table 10 shows causality assessment of individual ADR in control group.

Causality assessment was done using WHO-UMC causality assessment scale.

ADRs were categorized as either possible.

TABLE 11: CAUSALITY ASSESSMENT OF ADVERSE DRUG REACTIONS-STUDY GROUP

ADR	Certain	Probable	Possible	Un-likely	Un-classified	Un-classifiable
NAUSEA			1			
GASTRITIS			2			
MYALGIA						
PALPITATION						
PEDAL EDEMA		1				
HEADACHE			1			

Table 11 shows causality assessment of individual ADR in control group.

Causality assessment was done using WHO-UMC causality assessment scale.

ADRs were categorized as either possible.

TABLE 12: SEVERITY ASSESSMENT OF ADVERSE DRUG REACTIONS BY MODIFIED HARTWIG SIEGEL SCALE

SEVERITY	CONTROL GROUP	STUDY GROUP
MILD	7	5
MODERATE	-	-
SEVERE	-	-

Table 12 shows severity assessment of ADR by modified Hartwig Siegel scale.

All the ADR in control and study group were mild in severity.

Discussion

DISCUSSION

Hypertension, one of the leading causes of morbidity and mortality in both developing and developed countries. Hypertension when untreated, leads to various cardiovascular risks such as increased incidence of atherosclerosis, coronary artery disease and cerebrovascular risks such as stroke. It has been found that high blood pressure have been associated with increased incidence of stroke and other cardiovascular risks.

None of the anti-hypertensive drugs produce nitric oxide levels, which not only increases the arterial stiffness but also increases the risk of cardiovascular complications such as coronary artery disease and increased incidence of cerebrovascular accidents such as stroke.

Studies suggest that resveratol, a potent anti-oxidant by scavenging free radicals prevents the degradation of nitric oxide decreases the constrictor response of catecholamines and aids in the reduction of blood pressure. Hence the study was undertaken to find out the efficacy and tolerability of resveratrol as add on therapy to standard anti-hypertensive therapy in the reduction of blood pressure.

The study was conducted in the outpatient department of hypertensive clinic, department of internal medicine, madras medical college and government general hospital, Chennai.

Out of 97 screened 60 patients who fulfilled the inclusion and exclusion criteria were recruited for the study. They were randomized into two groups, Group l, Group ll, each group consisting of 30 patients. Group l received amlodipine 5mg OD Group ll received amlodipine 5mg OD with Resveratrol 100mg for a period of 4 weeks.

Efficacy variable such as systolic blood pressure and diastolic blood pressure were measured at the baseline, at the end of 2nd week at the end of 4th week of the study. Other hematological investigations such as complete hemogram, blood sugar, blood urea, serum creatinine, were done at the baseline, at the end of 2^{nd} week at the end of 4th week of the study and analyzed for any statistical significance. There is no statistical significance among the study groups in demographic characteristics.

In this study resveratrol in the dose of 100mg added with amlodipine produces significant decrease in systolic blood pressure at the end of 1 month.

Resveratrol at the dose of 100 mg when added with amlodipine 5mg OD causes statistical significant reduction of systolic blood pressure of 11.15% at the end od 1^{st} month of the study. Amlodipine 5mg OD alone group produces reduction of systolic blood pressure of 3.45% at the end of one month of the study.

In this study, resveratrol at the dose of 100 mg when added with amlodipine 5mg OD causes statistical significant reduction of diastolic blood pressure 12.72% at the end of one month of the study. Amlodipine 5mg OD alone group produces reduction of diastolic blood pressure of 7.08% at the end of one month of the study.

Other hematological and biochemical parameters were measured at the baseline, at the end of 2^{nd} week, and at the end of 4^{th} week found to have no statistical difference among the study groups.

Mild adverse effects such as nausea, vomiting, dyspepsia, diarrhea, dizziness, headache, cough and fatigue occurred among study groups which does not show any statistical significant difference (P=0.69) among the groups and all the adverse effect subsided without any medications.

Hence, resveratrol at the dose of 100mg / day along with amlodipine 5mg OD produces significant reduction of systolic and diastolic blood pressure to the desirable levels.

Conclusion

CONCLUSION

From our study, we conclude that;

- Resveratrol at the dose 100mg OD as an add on therapy to amlodipine 5mg OD causes significant reduction of both systolic and diastolic blood pressure.
- Resveratrol OD supplementation to the standard anti-hyperactive drugs may produce better reduction of blood pressure levels.
- Resveratrol may be recommended as an adjuvant to regular anti-hypertensive regimen to reduce cardiovascular and cerebrovascular risks associated with hypertension.

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Appendices

APPENDIX – I

ABBREVATIONS

AA	:	Ascorbic acid
ACE	:	Angiotensin converting enzyme
ADH	:	Anti diuretic hormone
ALT	:	Aspartate aminotransferase
ARBs	:	Angiotensin receptor blockers
ASD	:	Autism spectrum disorder
AST	:	Aspartate aminotransferase
BMI	:	Body Mass Index
BS	:	Blood Sugar
CD	:	Collecting duct
Cre	:	Creatintine
CRP	:	C-reactive protein
CVAs	:	Cerebrovascular accidents
CVD	:	Cardiovascular disease
DBP	:	Diastolic blood pressure
DCT	:	Distal convoluted tubule
dl	:	Deciliter
ELISA	:	Enzyme linked immunosorbent assay
Hb	:	Hemoglobin
HDL	:	High density lipoprotein

HT	:	Hypertension
ICAM-1	:	Intercellular adhesion molecule
IL-6	:	Interleukin 6
JAMA	:	The Journal of the American Medical Association
Kg	:	Kilogram
LDL	:	Low density lipoprotein
MCP-1	:	Monocyte chemoattractant protein
Mg	:	Milligram
MI	:	Myocardial infarction
Mm Hg	:	Millimeter of mercury
MR	:	Mineralocorticoid receptor
RA	:	Rheumatoid arthritis
RESV	:	Resveratrol
RTI	:	Respiratory tract infection
SAP	:	Serum alkaline phosphatase
SBP	:	Systolic blood pressure
SGOT	:	Serum glutamic oxaloacetic transaminase
SGPT	:	Serumglutamic pyruvic transaminase
TNF-α	:	Tumor necrosis factor α
TPR	:	Total peripheral resistance
Vit	:	Vitamin

APPENDIX – II

A PROSPECTIVE ,RANDOMIZED,OPEN LABEL,COMPARATIVE STUDY OF RESVERATROL IN SYSTEMIC HYPERTENSION

CASE REPORT FORM

NAME: Mr/Mrs AGE/SEX:

OP No: DIAGNOSIS:

ADDRESS: CONTACT NO.:

VISIT 1 (DAY 1)

PAST HISTORY:

ALLERGIC TO:

PERSONAL HISTORY:

CLINICAL EXAMINATION:

Ht: Wt:

VITAL SIGNS

Pulse rate: BP:

SYSTEMIC EXAMINATION

RS -

CVS -

ABDOMEN –

CNS -

LAB INVESTIGATIONS:

ECG

Fasting Blood sugar: mg/dl. Blood urea: mg/dl. Serum Creatinine: mg/dl.

Routine urine analysis: sugar albumin deposits

TREATMENT:

VISIT 2 (2nd week)

CLINICAL EXAMINATION:

VITAL SIGNS

Pulse rate: BP:

Adverse events:

VISIT 3 (4th week)

CLINICAL EXAMINATION:

VITAL SIGNS

Pulse rate: BP:

Adverse events:

VISIT 4 (8th week)

CLINICAL EXAMINATION:

VITAL SIGNS

Pulse rate: BP:

Adverse events:

Parameters	VISIT 1 (Day 1)	VISIT 2 (2^{nd} week)	VISIT 3 (4^{th} week)	VISIT 4 (8^{th} week)
Blood pressure				
Adverse events				
Date & Sign				

Name of the Doctor: Date:

Signature:

APPENDIX - III

INFORMED CONSENT FORM

Title: "A prospective ,randomized,open label,comparative study of resveratrol in systemic hypertension"

Name of the Participant:

I have read the information in this form(or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in this study.

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital.
6. I hereby give permission to the investigators to release the information obtained from me as a result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC.
7. I understand that my identity will be kept confidential if my data are publicly presented.
8. I have had my questions answered to my satisfaction.
9. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

1. Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

Name _____Signature _____Date_____

2. Name and signature of impartial witness (required for illiterate patients)

Name _____Signature _____Date_____

Address and contact number of the impartial witness:

3. Name and signature of the investigator or his representative obtaining consent:

Name _____Signature _____Date_____

APPENDIX - IV

Information to Participants

Title: "A prospective ,randomized,open label,comparative study of resveratrol in systemic hypertension"

Principal Investigator:

Name of Participant:

This study is being conducted in Hypertension OPD at Rajiv Gandhi Govt. General Hospital, Chennai. You are invited to take part in this study. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

What is the purpose of this study?

Hypertension is defined as abnormally high systolic and diastolic pressure. If hypertension remains untreated it can lead to a number of health problems like coronary heart disease, stroke, nephropathy, retinopathy, etc

Resveratrol is a naturally occurring flavanoid which has anti oxidant property. Resveratrol is useful in the control of blood pressure when added to a standard anti hypertensive therapy by increasing the production of nitric oxide (NO), an endogenous potent vasodilator. We want to test the efficacy and safety of treatment with resveratrol in reducing blood pressure. We have obtained permission from the Institutional Ethics Committee.

The study design:

All patients in the study will be divided into 2 groups A & B. You will be assigned to either of the groups. Group A will receive standard treatment & Group B will receive standard treatment + Resveratrol.

Study Procedures:

The study involves evaluation of control of blood pressure. The planned scheduled visits involve visits at 2^{nd}, 4^{th} & 8^{th} week after your initial visit. You will be required to visit the hospital 3 times during the study. At each visit, the study physician will monitor your blood pressure. Blood tests will be carried out during the beginning of the study and total of about 10 ml blood

will be collected. These tests are essential to assess the safety and efficacy of the treatment given to you.

In addition, if you notice any adverse events, you have to report it. You will be required to return unused study medicines when you report for your scheduled visits. This will enable correct assessment of the study results.

Possible benefits to you – Resveratrol along with standard treatment will cause reduction in blood pressure.

Possible benefits to other people - The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, and Institutional Ethics Committee to view your data, if required.The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. You will be taken care of and you will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment/discontinuing of procedures etc.

The expenditure for the treatment and investigation for this study will not be collected from you.

Signature of Investigator	Signature of Participant
Date	Date

சுய ஒப்புதல் படிவம்

ஆய்வு தலைப்பு

உயர் இரத்த அழுத்த சிகிச்சையில் ரெஸ்வரெட்ரால் பங்கு- ஓர் முன்னோக்கிய திறந்தநிலை ஒப்பிடுதல் ஆய்வு

பெயர் : தேதி :

வயது : உள் நோயாளி எண் :

..... என்பவராகிய நான் இந்த ஆய்வின் விவரங்களும் அதன் நோக்கங்களும் முறையாக அறிந்து கொண்டேன். எனது சந்தேகங்கள் அனைத்திற்கும் தகுந்த விளக்கம் அளிக்கப்பட்டது. இந்த ஆய்வில் முழு சுதந்திரத்துடன் மற்றும் சுய நினைவுடன் பங்கு கொள்ள சம்மதிக்கிறேன்.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் நன்கு புரிந்தகொண்டு எனது சம்மதத்தைத் தெரிவிக்கிறேன். இச்சுய ஒப்புதல் படிவத்தைப் பற்றி எனக்கு விளக்கப்பட்டது.

இந்த ஆய்வினை பற்றிய அனைத்து தகவல்களும் எனக்கு தெரிவிக்கப்பட்டது. இந்த ஆய்வில் எனது உரிமை மற்றும் பங்கினைப் பற்றி அறிந்து கொண்டேன்.

இந்த ஆய்வில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில்தான் பங்கு பெறுகிறேன் மற்றும் நான் இந்த ஆராய்ச்சியிலிருந்த எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.

இந்த ஆய்வில் கலந்து கொள்வதன் மூலம் என்னிடம் பெறப்படும் தகவலை ஆய்வாளர் இன்ஸ்டிட்யூசனல் எத்திக்ஸ் கமிட்டியினரிடமோ, அரசு நிறுவனத்தினடமோ தேவைப்பட்டால் பகிர்ந்து கொள்ளலாம் என சம்மதிக்கிறேன்.

இந்த ஆய்வின் முடிவுகளை வெளியிடும்போதே எனது பெயரோ, அடையாளமோ வெளியிடப்படாது என அறிந்து கொண்டேன். இந்த ஆய்வின் விவரங்களைக் கொண்ட தகவல் தாளைப் பெற்றுக் கொண்டேன். இந்த ஆய்விற்காக இரத்தப் பரிசோதனை செய்து கொள்ள சம்மதிக்கிறேன்.

இந்த ஆய்வில் பங்கேற்கும் பொழுது ஏதேனும் சந்தேகம் ஏற்பட்டால், உடனே ஆய்வாளரை தொடர்பு கொள்ள வேண்டும் என அறிந்து கொண்டேன்.

இச்சுய ஒப்புதல் படிவத்தில் கையெழுத்திடுவதன் மூலம் இதிலுள்ள அனைதது விஷயங்களும் எனக்கு தெளிவாக விளக்கப்பட்டது என்று தெரிவிக்கறேன். இச்சுய ஒப்புதல் படிவத்தின் ஒரு நகல் எனக்கு கொடுக்கப்படும் என்றும் தெரிந்து கொண்டேன்.

ஆய்வாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நாள் :

இடம் :

ஆய்வு தகவல் தாள்

ஆய்வு தலைப்பு : உயர் இரத்த அழுத்த சிகிச்சையில் ரெஸ்வரெட்ரால் பங்கு- ஓர் முன்னோக்கிய திறந்தநிலை ஒப்பிடுதல் ஆய்வு

ஆய்வாளர் :

பங்கேற்பாளர் :

இந்த ஆய்வு சென்னை இராஜீவ்காந்தி அரசு பொது மருத்துவமனையில் நடைபெற உள்ளது. நீங்களும் இந்த ஆய்வில் பங்கேற்க நாங்கள் விரும்புகிறோம். இதிலுள்ள தகவலின் அடிப்படையில் இந்த ஆய்வில் பங்கேற்பதா அல்லது வேண்டாமா என்று நீங்களே முடிவு செய்து கொள்ளலாம். உங்களது சந்தேகங்களை எங்களிடம் கேட்டு நிவர்த்தி செய்து கொள்ளலாம்.

இந்த ஆய்வின் நோக்கம் :

உயர் இரத்த அழுத்தம் என்பது அதிகமாக உள்ள சிஸ்டாலிக் மற்றும் டையஸ்டாலிக் அழுத்தமாகும். உயர் இரத்த அழுத்தத்தை சீர் செய்யவில்லை என்றால் அது இதய நோய், பக்கவாதம், சிறுநீரக குறைபாடு, கண் நோய் மற்றும் பல ஏற்படும்.

ரெஸ்வரெட்ரால் என்பது இயற்கையாக கிடைக்கக்கூடிய ஒரு பொருள். அதற்கு ஆன்டிஆக்ஸிடன்ட் தன்மை உள்ளது. ரெஸ்வரெட்ரால் உயர் இரத்த அழுத்தத்தை சீராக குறைக்கும் நைட்ரிக் ஆக்சைடு உற்பத்தி செய்வதால் இவ்வாறு செய்கிறது. உயர் இரத்த அழுத்தத்தை குறைப்பதில் ரெஸ்வரெட்டாலின் திறன் பற்றி அறிவதே இந்த ஆய்வின் நோக்கம் ஆகும்.

இந்த ஆய்விற்கு இன்ஸ்டிட்யூசனல் எத்திக்ஸ் கமிட்டி சம்மதம் பெற்றிருக்கிறோம்.

இந்த ஆய்வில் கலந்து கொள்பவர்கள் அ மற்றும் ஆ என்று இரு குழுக்களாகப் பிரிக்கப்படுவர். அ குழுவில் இருப்பவர்கள் வழக்கமான சிகிச்சையும், ஆ குழுவில் இருப்பவர்கள் வழக்கமான சிக்சையுடன் ரெஸ்வரெட்ரால் மருந்தும் பெறுவர்.

இந்த ஆய்வில் நீங்கள் முதல் வாரத்தில், இரண்டாவது வாரத்தில் மற்றும் 8வது வாரங்களில் பரிசோதிக்கப்படுவீர்கள். நோயின் தன்மையில் ஏற்படும் முன்னேற்றத்தினை அறிந்து கொள்வோம். இரண்டு முறை இரத்த அழுத்தம் பரிசோதனை செய்யப்படும். இந்த ஆய்வினில் ஏதேனும் பக்கவிளைவுகள் ஏற்பட்டால் உடனடியாக எங்களிடம் தெரிவிக்க வேண்டும்.

இந்த ஆய்வில் கலந்த கொள்வதன் மூலம் நீங்கள் நோயின் தன்மையில் முன்னேற்றம் பெறலாம். மேலும் வருங்காலத்தில் பிற நோயாளிகளும் பயன்பெற இந்த ஆய்வு உதவியாக அமையும்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும் போதோ அல்லது ஆய்வின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம். இந்த தகவல்தாளில் கையெழுத்திடுவதின் மூலம் உங்களைப்பற்றிய குறிப்புக்களையோ எடுத்துக்கொண்ட சிகிச்சை முறையை பற்றியோ, ஆய்வாளரோ, அல்லது இன்ஸ்ட்டியூசனல் எத்திக்ஸ் கமிட்யைச் சார்ந்தவர்களோ தேவை ஏற்பட்டால் அறிந்து கொள்ளலாம் என்று சம்மதிக்கிறீர்கள்.

இந்த ஆய்வில் பங்கேற்காவிட்டாலும், நீங்கள் வழக்கமான சிகிச்சையை தொடர்ந்து பெறலாம்.

இந்த ஆய்வில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆய்விலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்பு சிகிச்சையின் முடிவுகளை ஆய்வின் போதோ அல்லது ஆய்வின் முடிவின் போதோ தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆய்வில் தாங்கள் கலந்து கொள்வதால் சிகிச்சைக்காகவோ, இரத்த பரிசோதனைகளுக்காகவோ தங்களிடமிருந்து எந்த கட்டணமும் வசூலிக்கப்படமாட்டாது.

ஆய்வாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நாள் :
இடம் :

APPENDIX - V

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To

Dr.G.Selvam
I Year Post Graduate in MD Pharmacology
Institute of Pharmacology
Madras Medical College
Chennai 600 003

Dear Dr.G.Selvam,

The Institutional Ethics Committee has considered your request and approved your study titled **"A PROSPECTIVE, RANDOMIZED, OPEN LABEL, COMPARATIVE STUDY OF RESVERATROL IN SYSTEMIC HYPERTENSION " - NO.32062017**

The following members of Ethics Committee were present in the meeting hold on **06.06.2017** conducted at Madras Medical College, Chennai 3

1. Prof.Dr.C.Rajendran, MD.,	:Chairperson
2. Prof.R.Narayana Babu,MD.,DCH., MMC,Ch-3	: Deputy Chairperson
3. Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4. Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch	: Member
5.Prof.A.Pandiya Raj,Director, Inst. of Gen.Surgery,MMC	: Member
6.Prof.Rema Chandramohan,Prof.of Paediatrics,ICH,Chennai	: Member
7.Prof. Susila, Director, Inst. of Pharmacology,MMC,Ch-3	: Member
8.Prof.K.Ramadevi,MD., Director, Inst. of Bio-Chemistry,MMC,Ch-3	: Member
9.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
10.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist
11.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003